THE NATURAL HISTORY OF STROKE RECURRENCE AFTER FIRSTEVER STROKE

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THE NATURAL HISTORY OF STROKE RECURRENCE AFTER FIRST-EVER STROKE

THESIS

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Abstract of this thesis

Background - The natural history, predictors and outcomes of stroke recurrence after first-ever stroke have been insufficiently investigated. The available evidence shows great variation and does not provide a consensus of key predictors of stroke recurrence or a critical time-period for stroke recurrence occurring after initial stroke. This thesis uses data collected from the population-based South London Stroke Register to estimate the natural history of stroke recurrence after first-ever stroke.

Methods - Data were collected over 12 years from all individuals known to have had an initial and first recurrent stroke from the South London Stroke Register. The cumulative risk and predictors of stroke recurrence up to 12 years after first stroke were identified using survival analyses, taking into account the effect of temporal changes in stroke management. The effect of stroke recurrence on risk of death after first stroke was estimated up to 15 years after initial stroke. A systematic review and meta-analysis of studies of the risk and cumulative risk of stroke recurrence after first stroke was also conducted.

Results - The risk of stroke recurrence was estimated to be up to 25% at 12 years after first stroke. Cardiovascular risk factors were found to be important predictors of stroke recurrence, however differences in risk of recurrence were noted between the aetiological subtypes. Stroke recurrence was demonstrated to increase risk of death at all time-points up to 15 years after first stroke.

Conclusions – The risk of stroke recurrence is considerable and is associated with increased risk of death up to 15 years after first stroke. Further research is needed to examine the effect of secondary prevention on risk of recurrence. Recurrence in the first year after stroke may also be associated with the

biggest increase in risk of death identifying a potentially important time-period for stroke management to be targeted.

Table of Contents

Table of Figures

Table of Tables

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I am exceedingly grateful to Siobhan Crichton, not only for preparing the SLSR datasets, but for her patience, support and encouragement over the last 6 years. I am also grateful to my colleagues from the Division of Health and Social Care Research: Juliet Addo, Luis Ayerbe Garcia-Mozon, Anita Sheldenkar, Joanne Brooke, Kethakie Lamahewa and Nina Fudge,. Thanks to Dr. Patrick White, Dr. Alison Wright, Gill Cluckie, Helen Fisher, Helen Booth, Nimarta Darni, Jenny Nicholas and Christopher McKevitt for commenting on this thesis, and to Stania Kamara and Kiemu Salmon for their help

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Glossary of Abbreviations used in this thesis

AF	Atrial fibrillation
CE	Cardio-embolism
CI	Confidence Interval
CONC	Concurrent possible aetiology
DALY	Disability-adjusted life year
EPV	Events per variable
GCS	Glasgow Coma Score
HR	Hazard ratios
ICF	International Classification of Functioning, Disability and Health
ICH	Intracerebral haemorrhage
KM	Kaplan-Meier estimates
LAA	Large artery atherosclerosis
LACI	Lacunar Infarct
LDL	Low-density lipoprotein
MAR	Missing at random
MCAR	Missing completely at random
MI	Myocardial infarction
NA	No aetiology identified
NMAR	Missing not at random
OCSP	Oxford Community Stroke Project
ONS	Office for National Statistics
OR	Odds ratio
OTH	Other aetiology
PACI	Partial Anterior Circulation Infarct
PICH	Primary intracerebral haemorrhage
POCI	Posterior Circulation Infarct
RCP	Royal College of Physicians

SAH	Subarachnoid haemorrhage
SLSR	South London Stroke Register
SVD	Small vessel disease
SVO	Small vessel occlusion
TACI	Total Anterior Circulation Infarct
TIA	Transient Ischaemic Attack
TOAST	Trial of Org 10172 in Acute Stroke classification
UND	Undefined stroke subtype
WHO	World Health Organisation

Statement of contribution to thesis.

Chapter 1

This chapter was written by myself for the purposes of this thesis. Any published literature and policy related to stroke described in this chapter was reviewed by myself. The chapter was read and commented on by my supervisors Professor Charles Wolfe and Professor Janet Peacock. The aim and objectives of this thesis were derived by myself and discussed, and subsequently refined in conjunction with my then supervisors Professor Charles Wolfe and Professor Andy Grieve during my PhD upgrade viva.

Chapter 2

This chapter was written by myself for the purposes of this thesis. The description of the South London Stroke Register was reviewed by Professor Charles Wolfe, and the description of the statistical methods used in this thesis were reviewed by Professor Janet Peacock to ensure accuracy. The classification of stroke and stroke recurrence undertaken as part of this thesis using both the Oxford Community Stroke Project (OCSP) classification and the modified TOAST aetiological classification was undertaken by myself, however classification scores were verified by a Consultant Stroke Physician – namely Professor Anthony Rudd, Dr. Jonathan Birns or Dr. Ajay Bhalla.

Chapter 3

This chapter was written by myself for the purposes of this thesis, based on analyses undertaken and published in the *'Journal of Neurology Neurosurgery and Psychiatry'* in 2009. The statistical analyses described in this chapter were undertaken by myself under the supervision of Miss Siobhan Crichton, a statistician working at the South London Stroke Register. Whilst undertaking the analyses used in this chapter, I learned how to use the SPSS statistical package. At the time of the original paper being published the manuscript was

reviewed by Dr. Peter Heuschmann and Professor. Andy Grieve, who was my PhD supervisors at this time, as well as by Professor Anthony Rudd and Professor Charles Wolfe. During the writing up of these analyses for the purposes of this thesis, this chapter was reviewed by Professor Charles Wolfe and Professor Janet Peacock, who commented on both the content and structure of this chapter.

Chapter 4

This chapter was written by myself for the purposes of this thesis, based on analyses undertaken and published in *'Stroke'* in 2011. The literature searches and review was performed solely by myself, although my findings were discussed regularly with Professor Andy Grieve. The meta-analyses were undertaken by myself, again in regular discussion with Professor Grieve. The meta-regression model was performed in conjunction with Professor Grieve, who used this as as an opportunity to teach me how to develop a meta-regression model. At the time of the original paper being published the manuscript was also reviewed by Dr. Peter Heuschmann, Professor Anthony Rudd Professor Peter Kolominsky-Rabas and Professor Charles Wolfe. During the writing up of these analyses for the purposes of this thesis, this chapter was reviewed by Professor Charles Wolfe and Professor Janet Peacock, who commented on both the content and structure of this chapter

Chapter 5

This chapter was written by myself for the purposes of this thesis. All the analyses conducted in this thesis were undertaken by myself, under the supervision of Professor Andy Grieve. Having been taught how to develop the meta-regression model used in Chapter 4 of this thesis, I was able to develop the Exponential and Weibull models used in this chapter by myself. These were reviewed for accuracy by Professor Grieve. Prior to submission of this

thesis, this chapter was reviewed by Professor Charles Wolfe and Professor Janet Peacock who commented on both content and structure.

Chapter 6

This chapter was written by myself for the purposes of this thesis. All the analyses conducted in this chapter were undertaken by myself, and I taught myself to use SAS statistical package in order to develop the time-dependent covariates. The analyses conducted in this chapter were reviewed by Professor Janet Peacock when she became my PhD supervisor in April 2012. From that point on, Professor Peacock provided statistical supervision to this thesis. Prior to submission, Professor Charles Wolfe and Professor Janet Peacock reviewed this chapter and commented on both content and structure.

Chapter 7

This chapter was written by myself for the purposes of this thesis. The study was conceptualised by myself in discussion with Professor Charles Wolfe. All the statistical analyses conducted in this chapter were undertaken by myself, using STATA statistical package. The development of stroke recurrence as a time-dependent covariate was undertaken, after discussion with Professor Janet Peacock, under the supervision of Miss Siobhan Crichton, a statistician working at the South London Stroke Register. Prior to submission of this thesis, this chapter was reviewed by Professor Charles Wolfe and Professor Janet Peacock who commented on both content and structure.

Chapter 8

This concluding chapter was written by myself for the submission of this thesis. Prior to submission of this thesis, this chapter was reviewed by Professor Charles Wolfe and Professor Janet Peacock who commented on both content and structure.

Chapter 1 Introduction

Stroke is the second leading cause of global mortality and the third largest cause of disability worldwide [1, 2]. Whilst the impact of stroke on individuals and societies is undeniable, evidence from population-based studies on long-term outcomes after stroke remain relatively rare[3]. By using the population-based South London Stroke register (SLSR) as a sampling frame, this thesis will explore the natural history of stroke recurrence. Stroke recurrence is broadly defined as an individual's second stroke using criteria discussed later in this thesis.

This chapter provides the background for this thesis and sets out the concepts and ideas to be considered. It begins by describing the incidence of stroke from previous literature and presenting the outcomes experienced after first stroke, before focussing on stroke recurrence, the factors found to be important in predicting recurrence in previous literature, and how secondary prevention medication may have a role in reducing risk. The chapter concludes by outlining questions as yet unanswered by previous literature and explaining the objectives and hypothesis of this thesis.

1.1 The incidence of stroke

The World Health Organisation (WHO) estimated in 2002 (still the most recent published estimates) that 15.3 million people had a stroke worldwide, with more than a third, 5.5 million, resulting in death. Of the 57 million deaths worldwide in 2002, stroke accounted for nearly 10%[4]. Population projections for Europe suggest that the proportion of the population aged 65 and over will increase from 20% to 35% by 2050, and during the same time period, the total European population is expected to decrease from 728 million to 705 million[5]. It is predicted that this demographic shift will increase the number of acute stroke episodes from 1.1 to more than 1.5 million per year by 2025[6] and the WHO predict that stroke burden is projected to rise from around 38

million disability-adjusted life years (DALYs) globally in 1990 to 61 million DALYs by 2020[7].

However, data suggest that stroke incidence rates are not increasing in all countries and equally amongst all populations. Both data collected in men and women aged 35 to 64 years for the WHO MONICA Project, and population-based stroke studies, demonstrate a widening gap between high-income countries with low and declining stroke incidence and mortality rates, and in middle and low-income countries where stroke incidence and mortality is high and increasing[8-10]

Within the United Kingdom approximately 152000 strokes occur each year, including 30000 recurrent or second strokes. In 2010, stroke accounted for 50000 deaths in the UK (7% of all deaths in men and 10% of all deaths in women) [11]. Analyses conducted by Murray *et al* of the UK specific findings from the Global Burden of Disease Study 2010 showed that stroke remains the third highest cause of years of life lost across all ages in the UK, and a significant cause of both premature mortality and excess death when compared to other nations studied[12].

In 1999, Stewart *et al* reported age- and sex-adjusted stroke incidence rates of 1.25 per 1000 population per year in the geographically defined area covered by the South London Stroke Register (SLSR). They noted significantly higher incidence rates in black compared to white people with a black to white age-adjusted incidence rate ratio of 2.21. Their analyses revealed that in people aged 35-64, increasing age, male sex, black ethnic group and lower social class were independently associated with an increased incidence of stroke in South London[13]. More recently, SLSR analyses reported by Heuschmann *et al* demonstrated a total stroke incidence decrease of 18% in men from 1.57 to 1.29 per 1000 population and 24% in

women from 1.20 to 0.91 per 1000 population per year, over the 10 year study period between 1995-2004[14].

Decreasing trends in stroke incidence have also been reported by the other population-based stroke study in the United Kingdom. Stroke incidence rates in Oxfordshire from 1981 to 1984 and 2002 to 2004 were compared by the Oxford Vascular Study (OXVASC) in collaboration with the original investigators of the Oxfordshire Community Stroke Project (OCSP) There was little change reported in either the ethnic mix of the 93% white population or in the organisation of primary health-care during the interim period[15]. Despite a pre-study prediction of a 28% increase in first-ever strokes to account for the higher proportion of people aged over 75 years compared to the original study population, the observed number of strokes recorded decreased in both men and women. Age- and sex- adjusted incidence of first-ever stroke fell by 29% from 2.27 to 1.62 per 1000 population per year between the studies, and significant reductions were reported in the incidence of both disabling and fatal strokes[15]. This is consistent with decreasing trends in stroke incidence observed in the Global Burden of Disease analyses[12, 15].

1.2 The classification of stroke

It is widely accepted that stroke is not a single disorder but a heterogeneous collection of diseases, with approximately 85% of strokes due to cerebral infarction (ischaemic stroke), 10% due to primary haemorrhage (PICH) and 5% due to subarachnoid haemorrhage (SAH)[16]. Knowledge of the pathology and aetiology of a stroke can be important in order to understand why a stroke has occurred and to guide treatment choices, for example, the use of emergency thrombolysis to treat acute ischaemic stroke.

1.2.1 Ischaemic stroke

Ischaemic strokes occur due to an obstruction within a blood vessel supplying blood to the brain, mainly due to the development of atherosclerosis within

vessel walls. This can lead to the formation of a cerebral thrombosis at the site of the obstruction, an embolus which is carried to the brain inside the blood vessel, or the infarction of the small blood vessels deep inside the brain[17].

The estimated worldwide 30-day case fatality rate after first ischemic stroke ranges from 16 to 23% although wide variation has been reported in different countries and between different stroke subtypes[10, 18]

The two main classifications for ischaemic stroke used widely are the Oxford Community Stroke Project (OCSP) classification and the Trial of Org 10172 in Acute Stroke (TOAST) classification[19, 20]. The OCSP classification is a clinical classification used to allocate ischaemic strokes to one of four subtypes depending on the clinical signs and symptoms displayed at the time of maximum impairment after stroke. The four subtypes are: total anterior circulation stroke (TACI); partial anterior circulation stroke (PACI); lacunar infarct (LACI); and posterior circulation stroke (POCI). Details relating to how the subtypes are defined for the context of this thesis are discussed later in this thesis, however features of the four subtypes are summarised in Figure 1.

The TOAST classification divides ischaemic strokes into five main subtypes on the basis of probable or possible stroke aetiology using clinical features and the results of diagnostic tests. The five subtypes are: 1) large artery atherosclerosis, 2) cardioembolism, 3) small artery occlusion, 4) stroke of other determined aetiology, and 5) stroke of undetermined aetiology[20]. The strengths and limitations of this classification shall be discussed later in this thesis.

OCSP classification subtype	Clinical features
Total Anterior Circulation Infarct (TACI)	A combination of: • A new higher cerebral dysfunction (e.g., dysphasia, dyscalculia, visuospatial disorder); and • Homonymous visual field defect; and • Ipsilateral motor and/or sensory deficit of at least two areas of the face, arm and leg.
Partial Anterior Circulation Infarct (PACI)	Two of the three components of the TACI syndrome, with: • Higher cerebral dysfunction alone, or • A motor/sensory deficit more restricted than those classified as LACI
Lacunar Infarct (LACI)	• A pure motor stroke; • A pure sensory stroke; • A sensori-motor stroke; or Ataxic hemiparesis. • Acute focal movement disorders should also be considered with in this group.
Posterior Circulation Infarct (POCI)	Presentation with any of: • Ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit; bilateral motor and/or sensory deficit; • A disorder of conjugate eye movement; • Cerebellar dysfunction without ipsilateral long-tract deficit (i.e., ataxic hemiparesis); or • An isolated homonymous visual field defect.

Figure 1. The OCSP classification of stroke[19]

1.2.2 Primary intracerebral haemorrhage (PICH)

Primary intracerebral haemorrhage, or bleeding into the brain parenchyma is widely associated with poorer outcomes after stroke compared to the other stroke subtypes[21, 22]. The 30 day mortality for PICH has been reported to be 30‐55%, with half the deaths occurring in the acute phase, especially in the first 48 hours[23-25]. Complications of ICH also associated with poor outcome may include oedema, haematoma expansion or intra-ventricular extension with hydrocephalus, seizures and raised blood pressure[26].

1.2.3 Subarachnoid haemorrhage (SAH)

An SAH is a haemorrhage from a cerebral blood vessel, aneurysm or vascular malformation into the space between the arachnoid and pial layers of the brain. It is characterised by sudden onset headache, and vomiting, and may occur with or without loss of consciousness. 10–15% of those affected die before reaching hospital and 25% die within 24 hours of the bleed. Overall survival is about 50%, half of whom have residual disability and most of whom experience long-term effects of fatigue and cognitive symptoms[16].

1.3 Outcomes after first stroke

Knowledge of a patient's long-term prognosis for survival after a stroke is important to both patients and their clinicians. Prognostic information can help aid the selection of appropriate treatments for the patient and facilitate the provision of accurate information to the patient and their family [27].

Research from the Oxford Community Stroke Project (OCSP) found the 30 day all-stroke case fatality rate after first stroke to be 18%, with patients who survived at least 30 days having an average annual risk of mortality of 9.1%, over two times the risk of the general population[21, 28]. Adjusted mortality rates due to incident stroke (based on survival at one month) decreased by

37% from 0.44 per 1000 population (95%CI 0.35-0.54) during 1981-84 to 0.24 per 1000 population (95%CI 0.20-0.37) during 2002-2004. However, the 30 day case fatality recorded over this period remained the same: 17.2% in 2002-04 compared to 17.8 in 1981-84[15]. In South London, survival after first stroke was shown to improve significantly over a 16 year period between 1995 and 2010. In multivariable analyses, having had a recent stroke, being of black Caribbean/black African ethnicity, and stroke unit admission were found to be associated with better survival[29].

The impact of a stroke on the life of an individual is known to be an important predictor of outcome after first stroke. Often this can be taken to mean solely physical disability or stroke severity, however it has been known for over 20 years that social and psychological challenges can inhibit recovery after stroke[30]. The International Classification of Functioning, Disability and Health (ICF) was defined by the World Health Organisation (WHO) in 2001 as an attempt to provide a unified and standard language for defining health and health-related outcomes, taking into account all aspects of an individual's life, including their functional status and ability to participate in day-to-day activities[31]. After a stroke, patients and their carers are often faced with a multitude of physical, social and psychological challenges. Fifty percent of stroke survivors are left permanently disabled and requiring care either from relatives, friends or the community [32].

There are two main scales widely used to measure levels of disability and impairment after stroke. The modified Rankin scale has been reported to portray handicap, i.e. the disadvantage due to disability or impairment, by measuring an individual's functional independence. This contrasts with the Barthel Index, which estimates an individual's functional status through the ability to perform activities of daily living[33]. The scales are often used together or individually at regularly recorded intervals allowing functional improvement or decline to be quickly noted by clinicians.

A recent study by the Framingham Heart Study group, found that despite no significant difference in stroke subtype, severity and case-fatality rates, women were likely to be significantly more disabled. Disability was defined in the study using the modified Rankin score measuring functional independence, both at the time of stroke and during the acute phase (the first 14 days after stroke onset). This was found particularly in activities of dressing, grooming, and transfer from bed to chair. At three to six months after first stroke, women remained more disabled than men, and were 3.5 times more likely to be institutionalised[34].

Functional status, as defined using the Barthel Index, has been shown to be associated with quality of life after first stroke[35]. In a population-based study by Dhamoon et al in Northern Manhattan, USA, quality of life was shown to decline annually up to 5 years after stroke among survivors free of stroke recurrence or myocardial infarction and independent of other risk factors[35].

In analyses estimating disability, cognition and psychological outcomes up to 10 years after initial stroke between 1995 and 2006, Wolfe *et* al found that 20%–30% of survivors had a poor outcome over 10 years of follow-up. The highest rates of disability were observed 7 days after first stroke and remained at a rate of approximately 110 per 1000 stroke survivors up to 10 years. Rates of inactivity and cognitive impairment both declined up to 1 year thereafter remaining stable until eight years after stroke. Increased age was associated with higher rates of disability, inactivity, and cognitive impairment[3].

The long-term prognosis for recurrence-free survival is also of key importance[27]. Stroke survivors remain at increased risk of further strokes compared to the general population[36]. These recurrent strokes are more likely to be disabling or fatal than first strokes, yet studies show considerable variation in estimates of the cumulative risk of stroke recurrence in the early years and long-term after first stroke making it difficult for clinicians to begin to

predict an individual's risk of second stroke[37]. Differences in the reported risk of stroke recurrence and potential reasons for this shall be discussed further in Chapter 4.

1.4 Predictors of stroke recurrence

The lack of consensus regarding the prognostic indicators of stroke recurrence or second stroke, make it difficult for accurate identification of those at high risk of stroke recurrence particularly in the first weeks to months after first stroke [38, 39]. Chandratheva *et al,* on behalf of the Oxford Vascular Study, investigated the prognostic value of three widely-used validated prognostic scores: the ABCD(2) score, the Essen Stroke Risk Score and the Stroke Prognosis Instrument II on the 90 day risk of stroke recurrence. They found that the predictive power of the ABCD(2) score, which has a primary use predicting the risk of stroke after transient ischaemic attack, was at best modest in patients with a minor stroke. Neither the Essen Stroke Risk score nor the Stroke Prognosis Instrument II predicted stroke recurrence up to 90 days[39].

Even in the longer term problems with prognostic scores exist. The Essen Stroke Risk Score (ESRS), derived using data from a subset of ischaemic stroke patients in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, was shown to be predictive of recurrence at 1 year after first stroke, with a stepwise increase in risk demonstrated for every point increase in risk score[40]. However as the score predicts cardiovascular outcome rather than stroke recurrence, participants were considered to have had an 'initial event' if they had (1) symptomatic coronary artery disease; (2) cerebrovascular disease (ischemic stroke or TIA); (3) peripheral arterial disease; or (4) at least 3 predefined atherothrombotic risk factors. Furthermore, patients already in a clinical trial, hospitalized patients, those aged under 45 years age and those considered to have difficulty returning for a follow-up visit were excluded.

There remains a clear need for an accurate predictive model to estimate the risk of stroke recurrence in the short and long-term after first stroke. However, in order for this to be possible, identification of the factors important in stroke recurrence are first needed.

Despite being a major cause of mortality and morbidity, stroke remains largely preventable[41]. Studies have identified modifiable and non-modifiable risk factors associated with first stroke, which are summarised in Table 1.

Non-modifiable risk factors	Modifiable risk factors
Age	Hypertension
Sex	Diabetes
Ethnicity/race	Hyperlipidaemia
Family history of stroke	Atrial fibrillation
	Cigarette smoking
	Asymptomatic carotid stenosis
	Obesity
	Physical inactivity

Table 1. Risk factors for first stroke

To date, little consensus has been reached between studies as to which of these risk factors are important in predicting stroke recurrence. This shall be explored further in Chapter 3 of this thesis. Furthermore few population-based studies have looked at patterns of the pathological and aetiological stroke subtypes between first and second stroke during long-term follow-up i.e. 10 years and beyond. There is little evidence to indicate that if the subtype of a patient's first stroke is known, this can be used to predict the subtype of further strokes. This shall be discussed in Chapter 5 of this thesis.

1.5 The use of secondary prevention medication

Patients with a stroke recurrence are known to have, on average, poorer survival outcomes compared to those with a first stroke only. This was demonstrated in study by Samsa *et al* which estimated differences in 24-

month survival after first and recurrent stroke in the USA. They found survival from first stroke to consistently better than that for recurrent stroke (for example, the 2-year survival from first stroke for men aged 65 to 69 years was 66.5% after first stroke compared with 51.1% after recurrent stroke; p<0.001 by log-rank test and 68.0% versus 53.5% (p<0.001) for women of the same age). Overall 2 year survival was reported to be 48% after first stroke versus 56.7% (p<0.001) after stroke recurrence [42]. It therefore seems reasonable to hypothesise that appropriate secondary prevention needs to be implemented as soon as possible, and maintained beyond the first weeks and months after first stroke.

This is consistent with the National Clinical Guidelines for Stroke published by the Royal College of Physicians in 2012, however the number of trials supporting this hypothesis are fewer than for primary prevention[43, 44]. The non-randomised Early use of eXisting PREventive Strategies for Stroke (EXPRESS) study conducted by the Oxford Vascular Study group demonstrated that urgent assessment and treatment after TIA or minor stroke resulted in an 80% reduction in 90 day risk of recurrent stroke (adjusted hazard ratio 0·20, 95% CI 0·08–0·49; p=0·0001)[45].

However, secondary prevention has been shown in randomised controlled trial settings not merely to reduce the risk of recurrence, but to also have a role in reducing the overall cardiovascular disease burden by lowering mortality and morbidity rates[46]. Less evidence has been provided using population cohorts. It is notable that the studies mentioned below define a TIA as an initial cerebrovascular event rather than, as it will be defined later for the purposes of this thesis, as a pre-stroke risk factor.

1.5.1 Anti-hypertensive medication

In 1999, Hankey and Warlow reported that in a population of 1 million about 12000 would have had a previous stroke or TIA and 6000 (or 50%) of these will be hypertensive[47]. Since this time, many studies have investigated the effect of anti-hypertensive drugs in the secondary prevention of stroke. The key findings of two important studies are summarised below.

The HOPE study investigated the effect of ramipril in patients who were at high risk of cardiovascular events. Eleven percent of their included patients had a prior stroke, and this group showed a non-significant 17% relative risk reduction in stroke recurrence during the study period[48]. PROGRESS was a randomised trial of a perindopril-based blood pressure lowering regimen among 6105 individuals with a previous stroke or TIA. Patients were randomly assigned to either an active treatment group or placebo. After 4 years of follow-up, the risk of stroke was reduced by approximately 25% in both hypertensive and non-hypertensive subgroups[49]. More in depth analyses of ischaemic stroke subtypes, showed a significant benefit of active treatment with the combination of perindopril and indapamide in reducing atherosclerotic, lacunar and haemorrhagic strokes (relative risk reduction 39%, 23% and 50% respectively) with no effect noted on strokes of a cardio-embolic subtype[49].

1.5.2 Antiplatelet agents

Antiplatelet treatments such as aspirin, dipyridamole and clopidogrel have been shown to reduce the risk of recurrent stroke in clinical trials. The Antithrombotic Trialists Collaboration compared aspirin to placebo in a meta-analysis combining the results of 21 trials of people with a past history of stroke or TIA. The group reported a 2 year risk of 17.8% for those treated with antiplatelets and 21.4% for controls, therefore reporting a 22% odds reduction for non-fatal stroke or myocardial infarction or vascular death. The meta-analysis found that the risk reduction was the same regardless of whether a higher (greater than 75mg) or lower (less than 75mg) dose was given[50]. A

follow-up meta-analysis in 2009 by the same research group demonstrated a continued 20% risk reduction in stroke in patients taking aspirin compared to placebo[51].

1.5.2.1 Aspirin and dipyridamole

The results of the second European Stroke Prevention Study (ESPS-2) indicated that in the prevention of stroke after TIA or minor stroke, 200mg of extended-release dipyridamole taken twice a day was as effective as 25 mg of aspirin taken twice a day, with the combination of the two being even better than either drug alone. The relative risk reduction of stroke or death was 13% for aspirin, 15% for dipyridamole and 24% for the combination of the two drugs[52]. This was confirmed by the ESPRIT study which found an absolute risk reduction of 1% a year in a primary outcome measure (comprised of death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction or a major bleeding episode) in patients on aspirin and dipyridamole compared to aspirin alone[53].

1.5.2.2 Clopidogrel

As mentioned previously, the CAPRIE trial investigated the effect of clopidogrel compared to aspirin in patients with ischaemic stroke, myocardial infarction or peripheral vascular disease. They found that among the stroke sub-group, there was a 7.3% relative risk reduction of stroke, myocardial infarction or death[54]. The MATCH trial was conducted to investigate whether it was safe and more effective to add aspirin 75mg per day to clopidogrel 75mg per day in patients with recent TIA or ischaemic stroke who were at high risk of recurrent vascular events[55]. The study reported a benefit of 10 fewer recurrent ischaemic events per 1000 patients. However, there were three times as many life-threatening haemorrhages reported in the combined therapy group compared to those on clopidogrel alone[55].

1.5.3 Anti-coagulation

The oral anticoagulant warfarin, has been demonstrated to reduce the risk of cardio-embolic stroke, however it conveys no benefit compared to aspirin in patients with non-cardioembolic stroke[56].In patients with atrial fibrillation, the European Atrial Fibrillation Trial demonstrated that the use of warfarin therapy was associated with a risk reduction of 67% (from 12% to 4%) in patients with a previous TIA or minor stroke. The study also found an advantage in using warfarin over aspirin in these patients and clearly demonstrated that providing there is no known contraindication to its use, warfarin should be the treatment of choice[57].

1.5.4 Carotid revascularisation

Carotid endarterectomy has been shown to reduce the risk of recurrent stroke in patients with symptomatic stenosis, showing greater benefit in patients with a greater degree of stenosis until the vessel collapses and is occluded[58]. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) studied patients with a TIA or minor stroke and an ipsilateral carotid stenosis of 70% or more. The study found a 2 year risk of ipsilateral stroke was 9% in the endarterectomy group compared to 26% in those who were medically managed, and the trial was stopped early due to the significant benefit seen in the endarterectomy group[59]. However, the NASCET group found that the risk reduction was less in patients who have less severe carotid stenosis (50-69%). This was also found by the European Carotid Surgery Trial (ECST) who showed carotid endarterectomy to be of benefit for those with a high-grade carotid stenosis, defined as a 70-99% stenosis, but no benefit of surgery for those with a mild (0-29%) stenosis[60].

The treatment of carotid disease with angioplasty and stent placement has had mixed results when compared to the more traditional endarterectomy. The Carotid and Vertebral Artery Angioplasty Study found no significant

differences in risk of death due to stroke between the angioplasty and endarterectomy groups[61]. The Stenting and Angioplasty with Protection in Patients at High Risk of Endarterectomy (SAPPHIRE) study which included enrolled patients with a history of cardiac disease, showed the angioplasty group to have a better 30 day outcome, with stroke or death occurring in 4.5% compared to 6.6% of the endarterectomy group[62]. However, the largest trial comparing these procedures, the International Carotid Stenting Study (ICSS) reported twice the risk of stroke in the endovascular treatment group, compared to patients who underwent an endarterectomy (ICSS)[63]. Clearly more evidence is needed to necessitate a widespread change in practice from the traditional endarterectomy, to endovascular procedures in patients with no contra-indications[63].

1.5.5 Lipid-lowering agents

Studies indicate that lipid-lowering agents, traditionally used in patients with coronary artery disease, may be effective in independently reducing the risk of stroke recurrence. The Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) study was conducted to investigate the effect of aggressive atorvastatin therapy (80mg/day) on patients who had a previous TIA or stroke, had a low-density lipoprotein (LDL) level between 100 mg/dl and 190 mg/dl (2.58-4.91mmol/l) and had no evidence of coronary artery disease[64]. Patients were followed up for 6 years and a 16% risk reduction in time to stroke was demonstrated in the atorvastatin group, compared to the control group. A 23% risk reduction in the secondary end point of time to stroke or TIA and a 35% reduction in coronary events, were also noted. However, in this study, a 66% increased risk of intra-cerebral haemorrhage was found in the atorvastatin group. The mechanism for this is as yet undefined, and whilst the overall benefit in terms of stroke risk reduction is significant this is an area which requires further research[44, 64].

1.5.6 Others

Most studies investigating the risk of glycaemic control in patients with diabetes mellitus have looked at primary rather than secondary prevention[65, 66]. However, pioglitazone, one of the insulin sensitiser thiazolidinediones was shown to reduce insulin resistance in diabetic patients with a recent stroke or TIA[67]. The safety profile of the thazolidinediones have come under scrutiny in recent years with the withdrawal of rosaglitazone for increasing cardiovascular risk, although pioglitazone was not implicated at this time[68].

There are no published studies specifically reporting the role of smoking cessation, abstinence from alcohol, weight reduction measures, or physical activity in risk reduction for stroke recurrence.

1.6 Problems with the use of secondary prevention

Despite the evidence mounting for the use of secondary prevention to reduce the risk of recurrent stroke, it is apparent that not all patients who would benefit from these medications, receive or take them. A national cross-sectional study of nursing homes in the United States found that when adjusted for age, sex and physical function, black stroke survivors were 20% less likely to receive any form of anticoagulant or antiplatelet therapy compared to white survivors[69]. The study also noted that the use of any treatment was lower for Hispanics (45.5%), non-Hispanic blacks (49.4%) and Asian-Pacific Islanders (38.9%) than for whites (54.3%), although they were higher amongst the Native American population (58.0%). This is despite long-standing evidence that the black and Hispanic population have an increased risk of stroke recurrence compared to the white population[70].

Problems in initiating secondary preventive strategies include patient compliance due to undesired side-effects, poor understanding, financial constraints and poor motivation, as well as inadequate communication and a lack of motivation and reinforcement from health professionals [71, 72]

The second national health and nutrition examination survey (NHANES) mortality follow-up study demonstrated a stepwise increase in cardiovascular disease mortality for patients with a previous history of myocardial infarction or stroke with increasing numbers of inadequately controlled risk factors. For patients with a previous history of MI or stroke the relative risk of cardiovascular death was reported as 2.6 (95% CI 1.3-5.1) times the general population if all investigated risk factors were adequately controlled, increasing to 4.3 (2.9-6.3) times with one inadequately controlled risk factor, and 5.7 times the risk of death with two inadequately controlled risk factors. This equates to 5.7 years of life lost compared to the age-matched general population even if all risk factors are controlled, increasing to 7.5 years and 8.9 years lost with one and two inadequately controlled risk factors respectively [73].

Knowing an individual's risk of stroke recurrence, based on their personal risk factor profile may provide a stroke survivor with the impetus for risk factor modification[74]. It may also help health professionals to identify those at increased risk, possibly from multiple borderline risk factors which individually may seemingly not be cause for concern. This is critical in identifying and targeting specific risk factors important for an individual at the crucial time-point after first stroke, therefore reducing the risk of stroke recurrence at an individual patient level.

1.7 Unanswered questions

Despite the previous research conducted on stroke recurrence, many questions remain as yet unanswered. In particular:

- What is the risk of stroke recurrence for an individual at different time points after first stroke?
- Which risk factors are important in predicting stroke recurrence for an individual?

- Are the important risk factors for stroke recurrence different up to 1 year, 5 years and 10 years after first stroke?

- Is targeted use of secondary prevention likely to reduce the risk of stroke recurrence in high-risk individuals?
- What is the effect of stroke recurrence on other outcomes, for example the risk of death after first stroke?
- Is risk of death dependent on the time-point at which stroke recurrence occurs?

1.8 Hypothesis

This thesis hypothesises that:

- the natural history of stroke recurrence can be estimated, and predictors of stroke recurrence can be identified at different time points up to 12 years after first-ever stroke.
- the treatment of modifiable predictors of stroke recurrence, at the appropriate time point after stroke recurrence will reduce the risk of stroke recurrence.
- stroke recurrence has an effect on risk of death after first-ever stroke.

1.9 Objectives of thesis

This thesis will use data collected from the South London Stroke Register, to estimate the natural history of stroke recurrence after first-ever stroke. Predictors for stroke recurrence will then be identified from variables including socio-demographic factors, risk factors diagnosed at the time of initial stroke, patterns in stroke subtype, and stroke severity markers, taking into account the effect of temporal changes in stroke management, e.g. the use of secondary prevention medication.

This shall be addressed through the analysis of data collected over a period of 12 years from all individuals known to have had an initial and first recurrent stroke from within the South London Stroke Register, a population-based

stroke register situated in a geographically defined area of South London. The objectives of this thesis are:

1. To estimate the cumulative risk of stroke recurrence at different time-points up to 12 years after first-ever stroke from existing literature and from a population-based stroke register.

2. To identify factors which predict the risk of stroke recurrence, from variables including socio-demographic factors, risk factors diagnosed at the time of initial stroke, patterns in stroke subtype, and stroke severity markers, at different time-points up to 12 years after first-ever stroke.

3. To investigate the association of temporal changes in stroke management, e.g. the use of secondary prevention medication at different time-points after initial stroke, on the risk of stroke recurrence.

4. To estimate the association between stroke recurrence and the risk of death up to 15 years after first-ever stroke.

1.10 Summary

This chapter has highlighted gaps in current literature related to stroke recurrence, and demonstrated the need to explore the natural history of stroke recurrence further and to identify predictors. It seems logical to hypothesise that appropriate secondary prevention medication should reduce the risk of stroke recurrence by targeting important risk factors.

The next chapter outlines the South London Stroke Register which is the sampling frame from which the analyses presented in this thesis were conducted. The methods used in both the literature review searches, and for the statistical analyses undertaken in this thesis are also described.

Chapter 2. Methods

This chapter builds on the background laid out in Chapter 1 of this thesis. It outlines the rationale for using a population-based register as a sampling frame to measure the impact of stroke, and describes the characteristics of the South London Stroke Register, which shall be used to fulfil the objectives described in the previous chapter. The search strategies and methods used to review the literature and conduct the meta-analysis are then described. Finally, the general statistical methods used in the analyses for this thesis shall be outlined.

2.1 Population-based stroke registers

The measurement of the overall health status of a population is an important public health issue, and it is essential that methods used to measure the impact of illness fully reflect the effect of disease on the whole of the population being studied. Whilst hospital-based studies measuring outcome after chronic disease may have access to a readily available cohort of patients with the condition of interest to the researchers, many are restricted to selected patients, such as those admitted to hospital or referred to rehabilitation services.

There are several major disadvantages to the use of hospital-based studies or registers to assess outcome after stroke due to distortion of the true clinical course and prognosis by selection bias. A key disadvantage is the degree to which the case-mix of hospital-based studies can be representative of stroke patients as a whole, and therefore how far information obtained can be extrapolated to other groups of patients. Or particular concern is the inclusion of both severely ill patients and those with mild stroke symptoms, both of whom may not be admitted to hospital for a variety of reasons[75]. This will be discussed in more detail as part of the systematic review in Chapter 4. Non-population-based studies also have epidemiological limitations as they lack a

reliable denominator, therefore precluding the calculation of incidence rates[76].

In 1987, Malmgren and colleagues, reviewed 65 studies of stroke incidence from around the world and found that only nine studies met a set of standardised criteria sufficiently to allow comparison with each other[77]. These criteria have been updated by Bonita in 1995, and Sudlow and Warlow in 1996 to produce an updated set of criteria for comparable studies of stroke incidence[75][72].

These criteria are summarised in Table 2.

Standard definitions • WHO definitions of stroke • First-ever-in-a-lifetime stroke data available, even if unpublished
Standard methods • Complete, community-based case ascertainment • Prospective study design, ideally with 'hot pursuit'' of cases • Large, well-defined, stable population • Reliable method for estimating population denominator
Standard data • Separate whole years of data available, even if unpublished • Data for men and women separately available, even if unpublished • Include ages up to and over 85 years if possible • Standard mid-decade age-bands) e.g.. 55-64 years) available, even if unpublished • Data preferably available in 5-year age bands

Table 2. Criteria for Comparable Studies of Stroke Incidence[75]

2.2 The South London Stroke Register (SLSR)

The SLSR is a prospective, longitudinal, population-based stroke register recording first-ever strokes in patients of all age groups in a defined area of South London. Since 1 January 1995, the SLSR has been monitoring incidence rates, cause, risk factors and long-term outcomes after stroke[13].

The SLSR provides a good sampling frame for this thesis as it provides long-term longitudinal data from a population-based setting, using overlapping notification sources and capture-recapture techniques in order to maximise completeness of case ascertainment[14]. Follow-up data are collected at multiple time-points making it possible to conduct longitudinal comparisons of stroke outcomes over time. Therefore it is possible to use the SLSR to describe the natural history of stroke recurrence as well as to assess the development of risk factors for stroke recurrence over time.

The SLSR has all the criteria listed in Table 2 as essential for a population-based stroke register[75]. These include:

- a clear and concise implementation plan and SLSR manual to ensure quality control of the data;
- 'hot pursuit' of cases to maximise case ascertainment;
- multiple overlapping sources of notification to maximise completeness of case ascertainment;
- commitment from local medical practitioners including local hospital consultants and general practitioners, regarding case notification;
- effective methods of data collection and processing
- adequate safeguarding procedures to ensure confidentiality of information obtained in the SLSR.

As with any long-term disease register, there are certain limitations which need to be acknowledged:

- It is highly likely that despite overlapping notification sources and 'hot-pursuit' techniques, there are cases that will not be identified by the SLSR, including those who had a stroke whilst away from home, and those who sustained minor strokes and may not have sought help from either their general practitioner or secondary care services[13].

- Although population denominator data was derived from census data from the Office for National Statistics (ONS), the area of South London in which the SLSR is situated has a highly transient population. Southwark in particular was cited as one of the ten London boroughs with the highest levels of population mobility between 1991 and 2001[78]. For this reason, population growth, mobility and cross boundary effects are difficult to estimate within this area and may influence results derived from the SLSR.

- Due to the length of follow-up undertaken at the SLSR (currently in its 19th year), is it inevitable that there will be missing data due to reasons including retrospective registrations, loss to follow-up, refusal by the patient or carer, or a basic lack of known data available to the SLSR. The methods of limiting and handling of missing data used in this thesis are discussed in Section 2.5.

- As a practical consideration of note, issues with the continuity of data collection due to the long duration of the SLSR are inevitable. This is due to changeover of staff at the SLSR over time, and changes to the data collected by the register over the last 19 years. The methods used to limit the effect of the latter on this thesis are discussed in Section

2.5, however the regularly updated SLSR manual is a useful aid to overcome these limitations to a certain degree.

2.2.1 The SLSR population

The SLSR records first stroke in patients of all age groups living within a defined area corresponding to 22 wards of Lambeth and Southwark . The total source population was 271817 with 63% white, 28% black and 9% of other ethnic groups at the time of Census 2001[79].

In 2004 the boundaries of the SLSR area were changed to reflect boundaries of electoral wards as defined at that time. The new area consisted of 310,026 persons at the time of the 2001 census, 14.1% more than the old area, estimated to have a population of 271,817 in 2001. Between 2001 and 2011 the population of the new area increased by 15.3%, with the largest increases occurring among 45 to 59 year olds (44% increase), Asian (51% increase) and other (232% increase) ethnic groups

At the time of the 2011 census the SLSR source population consisted of 357,308 individuals of which 56% were of white ethnicity, 25% Black (14% Black African, 7% black Caribbean, 4 % Black Other), 6% Asian and 12% other ethnic group. [80]. Table 3 shows the ethnicity breakdown for the SLSR area. It is notable that the proportion of the study population who were of a Black Caribbean ethnicity, declined through throughout the study period, whilst the Black African population substantially increased.

	1991	2001 (new boundaries)	2011
	Total (%)	Total (%)	Total (%)
All white	167834 (72.6)	194177 (62.3)	200890 (56.2)
Black African	17477 (7.5)	46104 (14.9)	50556 (14.1)
Black Carribean	25809 (11.0)	29011 (9.4)	25087 (7.0)
Black other	6213 (2.7)	13498 (4.4)	15315 (4.3)
Asian*	(In 'Other' in 1991)	13880 (4.5)	21023 (5.9)
Other	17200 (7.3)	13356 (4.3)	44437 (12.4)
Total	234533	310026	357308

Table 3: Ethnicity breakdown for SLSR area in the 1991, 2001 and 2011 census

2.2.2 Case ascertainment

The SLSR utilises multiple overlapping referral sources to ensure notification of all patients with a suspected diagnosis of first or recurrent stroke[13]. 'Hot pursuit' is used to detect stroke cases, i.e. SLSR staff actively pursue potential stroke cases, rather than waiting passively for referrals to the register from notification sources. Patients identified by any notification source, are investigated for eligibility of study inclusion. Hospital surveillance of admissions for stroke include teaching hospitals both within and outside the study area. For identifying patients not admitted to hospital, all general practitioners (GPs) and community therapists within and on the borders of the study area are contacted regularly and asked to notify all potential stroke patients to the SLSR[13]. Completeness of case ascertainment was estimated to be between 75-84% over the 10 year period from 1995-2004[14]. The sources of notification include:

- Research team/ward checks

Telephone contact is made twice-weekly with all wards at St. Thomas Hospital, Guy's Hospital and King's College Hospital, and once a week with

the wards at St. George's Hospital, University Hospital Lewisham and the National Hospital for Neurology and Neurosurgery at Queen Square. SLSR staff also regularly visit the hospital wards where stroke patients are most likely to be admitted, such as stroke units, neurosurgery wards, medical admissions units, and rehabilitation wards in order to identify any patients suitable for admission to the SLSR.

- Hospital staff

Consultants, junior doctors and nursing staff, particularly those working in stroke medicine, neurology or neurosurgery, elderly care medicine or general medicine are encouraged to notify any patients they may see in their clinical practice, both as in-patients and out-patients.

- Radiology electronic records

The results of CT and MRI scans of the brain conducted at Guy's and St. Thomas', King's College Hospital and St. Georges Hospital are viewed electronically by a Research Registrar to identify any potential strokes cases. Once screened, the relevant notes are retrieved for possible stroke diagnosis. Cases where a diagnosis of stroke is possible but unclear are discussed with a Stroke Consultant before a final decision whether to proceed with stroke registration, or not, is made.

- Accident and Emergency (A&E) records

These records, in particular those of hospital admissions maintained by Bed Managers at St. Thomas' Hospital and King's College Hospital, are regularly checked for any stroke cases admitted to hospital. A&E records can also be particularly useful for identifying stroke patients who died very soon after admission to hospital, as well as patients presenting to hospital with very minor symptoms discharged directly from A&E, particularly at the weekend.

- Bereavement records

Records in the bereavement office at St. Thomas' and King's College Hospitals are regularly checked for the mention of stroke on any part of the death certificate. The notes of all patients where stroke is mentioned are then examined to identify any suitable cases not previously known to the SLSR.

- General Practitioner and practice staff

GP surgeries notify the SLSR of any relevant stroke cases by telephone, electronic mail or by post. In order to make local GPs aware of the SLSR and keep them informed of any changes to the register, all GPs are sent a newsletter from the SLSR every three months. SLSR staff also request consent from stroke patients or their carers to report all incident cases back to the patient's own GP to keep them as informed as possible.

- Community therapists

Therapists from the local community hospitals (Lambeth Community Care Centre and Pulross) notify the SLSR of any stroke cases referred to them. Regular newsletters are also sent to keep the community therapists up to date about the SLSR.

- Office for National Statistics (ONS)

An updated list is sent every six months to the ONS of all patients on the SLSR who were alive, or who were known to have died but for whom there was no death record reviewed by SLSR staff. The ONS inform the SLSR on a quarterly basis of any of these patients who have died. The ONS also provide death certificate data which can be reviewed by SLSR staff to ascertain the documented cause of death. In the context of this thesis, this was particularly

useful to ascertain stroke recurrence prior to death in patients known to the SLSR.

2.2.3 Data collection

Specially trained fieldworkers collect all reported data prospectively. Initial assessments are performed within 72 hours of onset of stroke symptoms wherever possible. Data are collected from patients, their relatives, friends, carers, and where necessary from their medical notes or general practitioner allowing pre-stroke information to be collected for even the most dysphasic, confused or unwell patients. Difficult cases are discussed with senior stroke physicians prior to registration, and all registered cases are reviewed on a monthly basis in order to monitor inter-observer validity and to ensure that the stroke subtypes recorded are appropriate. The information collected on initial assessment includes patient demography, stroke risk factors, indicators of stroke severity, and stroke subtypes according to pathological and aetiological classification.

After the initial interview, patients registered at the SLSR are followed up at three months, one year, and then annually post-initial stroke. In all but very few cases, these assessments are carried out by a field-worker by face-to-face interview with the patient and/or their carers. However in order to follow-up patients who may not be able to be visited by fieldworkers, e.g. those who move far away from the study area either after initial stroke or during the follow-up period, both postal and telephone versions of the follow-up questionnaire have been designed. The follow-up questionnaires are standardised into an easy-to-read format to enable patients to fill in the questions themselves. Questionnaires for each time point are identical to allow longitudinal comparisons to be made.

2.2.4 Ethical approval

Informed consent to participate in the SLSR is obtained from all recruited patients, or assent from their designated next of kin if the patient is unable to consent themselves. The design of the SLSR is approved by the NHS Research Ethics Committees of Guy's and St Thomas' NHS Foundation Trust (REC number: EC01/020), King's College Hospital Foundation Trust, St George's University Hospital, National Hospital for Neurology and Neurosurgery, and Westminster Hospital.

2.3 Variable definition

All explanatory and response variables used in this thesis are defined fully in the later chapters, however a brief summary of the variables used is given below.

2.3.1 Defining stroke and stroke recurrence

For the purposes of the original analyses conducted in this thesis, a stroke has been defined according to the World Health Organisation (WHO) criteria as:

'Rapidly developing clinical signs of focal (or global) neurological deficit lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin'[81].

A stroke recurrence has been defined in the same way as for an initial stroke, however in addition for a diagnosis of a recurrence to be made, the presence of a new neurological deficit, or deterioration of a previous deficit not due to oedema, haemorrhagic transformation, or intercurrent illness is required. Only recurrences 21 days after the initial event, or if earlier, clearly in a different vascular territory are included in the SLSR and therefore only after this time or

in these circumstances shall be included in the analyses conducted in this thesis. Differences in the definitions of stroke recurrence used in studies shall be discussed further in Chapter 4, later in this thesis.

2.3.2 Classifications of stroke subtype

The main pathological and aetiological subtypes widely used to classify stroke were described earlier in this thesis in Section 1.2. The pathological subtype of stroke will be classified using the broad categories of the Oxfordshire Community Stroke Project (OCSP) classification as cerebral infarction (CI), primary intracerebral haemorrhage (PICH), subarachnoid haemorrhage (SAH) or undefined (UND)[19]. Classification is based on results from at least one of the following: brain imaging performed within 30 days of stroke (computerised tomography or magnetic resonance imaging), analysis of cerebrospinal fluid (in all living patients with subarachnoid haemorrhage in whom brain imaging was not diagnostic) or necropsy examination.

The aetiological classification of ischaemic strokes will use a classification system based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[20], modified in order to improve the rate of determined aetiology and to account for expected differences in stroke subtype for the local black population[82]. A summary of the modified TOAST criteria is shown in Table 4.

Stroke subtypes include extracranial large artery atherosclerosis (LAAec), intracranial large artery atherosclerosis (LAAic), high-risk cardioembolism (CE-h), medium-risk cardioembolism (CE-m), small vessel occlusion (SVO), no aetiology identified (NA) and concurrent possible aetiology (CONC).

Stroke subtype	Clinical findings	Brain imaging (CT/MRI)	Carotid imaging (Doppler/TCD/Angiography)	Cardiac imaging (ECG/TTE/TOE)	Past medical history/other investigations
LAA (ec)	WHO definition of stroke	Infarct >1.5 cm diameter	≥50% stenosis of extracranial artery	No high- or medium-risk cardiac embolic source	–
LAA (ic)	WHO definition of stroke	Infarct >1.5 cm diameter	≥50% stenosis of intracranial artery	No high- or medium-risk cardiac embolic source	–
CE-h	WHO definition of stroke	Infarct >1.5 cm diameter	No significant atherosclerotic disease	High-risk cardiac embolic source	High-risk cardiac embolic source
CE-m	WHO definition of stroke	Infarct >1.5 cm diameter	No significant atherosclerotic disease	Medium-risk cardiac embolic source	Medium-risk cardiac embolic source
SVO	Clinical lacunar syndrome	Brainstem/subcortical infarct ≤1.5 cm	No significant atherosclerotic disease	No high-risk cardiac embolic source	–
OTH	WHO definition of stroke	Infarct in any location of any size	No significant atherosclerotic disease	No high- or medium-risk cardiac embolic source	Other aetiology identified
NA	WHO definition of stroke	Infarct in any location of any size	No significant atherosclerotic disease	No high- or medium-risk cardiac embolic source	–
CONC	As per individual aetiologies	As per individual aetiologies	As per individual aetiologies	As per individual aetiologies	As per individual aetiologies

Table 4 Summary of criteria for the aetiological classification of patients with ischaemic stroke[82]

LAAec: extracranial large artery atherosclerosis; LAAic: intracranial large artery atherosclerosis; CH: high-risk cardioembolism; CM: medium-risk cardioembolism; SVO: small vessel occlusion; OTH: other aetiology; NA: no aetiology; CONC: multiple probable or multiple possible aetiology. The latter category includes patients for whom two aetiologies of equal weighting are identified.

2.3.3 Case ascertainment of stroke recurrence

Stroke recurrence was ascertained in the same way as for initial stroke, by use of the referral sources discussed in Section 2.2.2. In addition all patients followed up annually by the SLSR were asked the following screening questions to ascertain if they had had a recurrence:

- Have you had another stroke since your last follow up visit or since your first stroke?
- Have you experienced any of the following symptoms: new visual problems, new speech problems, or new weakness of your arms and legs, since your last follow-up visit or since your first stroke?

If the patient was found to have had a stroke recurrence, according to the criteria defined in Section 2.3.1, a form documenting details of the stroke recurrence was completed by the fieldworker. Registration of first stroke recurrence was performed in the same way as the initial stroke

2.3.4 The main explanatory variables used in this thesis

Potential predictors of stroke recurrence were identified through review of the literature and the following variables were selected:

Demographic factors included age (categorised as <65, 65-74, ≥75), gender, ethnicity (categorised as white, black and other) and socio-economic status. Socioeconomic status categories were grouped into non-manual (I, II, and III non-manual) or manual (III manual, IV, and V) or economically inactive, according to the patient's current (or for the retired and others not currently working, the most recent) employment[83].

Information about co-morbidities, obtained from the initial questionnaire or from GP records, included history of transient ischaemic attack (TIA), ischaemic heart disease, atrial fibrillation (AF), hypertension, diabetes mellitus and smoking. Smoking status was recorded as current smoker or non- or ex-smoker.

Stroke severity was defined as the presence of neurological deficit during the acute phase of the initial stroke. The level of consciousness was assessed using the Glasgow Coma Scale (GCS) dichotomized into GCS <13 (impaired consciousness) and GCS≥13[84].

Classification of pathological stroke subtype was categorised into ischaemic stroke, PICH or SAH based on results from at least one of the following: brain imaging (CT or MRI scan) and post-mortem studies.

A range of indicators of the processes of care after an acute stroke, suggested to be useful proxy measures for the overall quality of stroke care, were examined[16]. Patients were classified as (1) not admitted to hospital; (2) admitted to stroke unit; (3) admitted to general medical ward/intensive care; and (4) unknown.

2.4 My personal contribution and experience at the SLSR

I worked for four years (2007-2011) as a Clinical Research Fellow on the SLSR. During this time, my position has been split between working as a member of the SLSR team, and my involvement in the research project from which the work contributing to this thesis is derived. I gained practical understanding of general research methodology, as well as first-hand experience of the benefits and challenges of working on a longitudinal study such as the SLSR. In particular:

- I confirmed the diagnosis of new stroke cases referred to the register and discussed any difficult cases with senior stroke physicians before completing the initial assessment forms.

- I identified stroke cases by visiting medical wards, elderly care wards, stroke units and the bereavement offices of Guy's and St. Thomas', King's College Hospital, and St. George's Hospital.

- I gained experience in interpreting CT and MRI brain scans and benefitted from one-to-one review of these radiological assessments with expert stroke physicians. I also attended multi-disciplinary team meetings on the stroke unit, and participated in stroke clinics.

- I conducted three-monthly and annual follow-up assessments of patients by both face to face and telephone interviews. This allowed me to better understand many of the long-term challenges faced by stroke survivors in the community.

- I participated in the re-design of the initial and recurrence assessment questionnaires. The regular review of the questionnaires allows the SLSR to optimise the questions being asked of register participants and tailor the questionnaire to match current research aims. This also stops the questionnaire getting too long, an important factor for ensuring the maximum response rate.

- I learned the principles of epidemiology and statistics, including data entry, collection, analysis and interpretation. The analyses undertaken in this thesis use three statistical packages 'SPSS', 'STATA' and 'SAS'. This is because during the course of this thesis I learned how to use each of these

packages and learned to conduct all the univariate and multivariable analyses described in this thesis. This includes both time-dependent and non-time-dependent survival analyses.

- I have presented findings from this thesis in the form of oral and poster presentations at national and international stroke conferences, have written papers in peer-reviewed journals, contributed to book chapters, and lectured both medical students, doctors, other researchers and PhD students about stroke epidemiology, stroke recurrence and the use of secondary prevention.

2.5 Handling missing data

Due to the length of follow-up of patients undertaken at the SLSR, there will invariably be missing data. Data may be missing completely at random (MCAR), missing at random (MAR) or missing not at random (NMAR)[85]. If data are MCAR or MAR, they can be analysed as normal, (using maximum likelihood methods) and should give unbiased results, providing all variables associated with a chance of missing a measurement are included in the model[85]. However this is not true of NMAR data, and any analyses conducted using this data may be biased.

Within the SLSR, reasons for missing data during follow-up include retrospective registrations; patients lost to follow up either for a specific time interval i.e. missing their two year follow-up only, or indefinitely; or very rarely, due to refusal but the patient or their carers. The analyses conducted in Chapter 3 of this thesis, used data collected at the time of initial stroke and subsequent follow-up assessments, for initial strokes registered with the SLSR from 1995-2005.

During this thesis, analyses were not specifically undertaken to assess whether loss to follow-up was uninformative with regards to stroke recurrence, i.e. whether patient groups with certain characteristics were more or less likely to be lost to

follow-up. However in as yet unpublished work looking at predictors of being lost to follow-up within the SLSR population, no differences in odds were reported between the ethnic groups.

Whilst data has been collected on both initial and recurrent stroke by the SLSR since 1995, it became evident that in order to have sufficient long-term data needed for the more complex analyses later in this thesis, the original data sources would need to be reviewed. Therefore I also undertook different measures specifically related to maximising the completeness of available data related to patients with a stroke recurrence:

- I conducted a review of the data related specifically to stroke recurrence collected by the SLSR since January 1995. The purpose of this review was to primarily access the medical records, including those transferred to microfiche for storage, of all patients who were known to the SLSR as having had a stroke recurrence. This allowed the information previously obtained on SLSR recurrence forms to be verified, and any additional information identified to be available for use in subsequent analyses.

- Both the pathological OCSP and aetiological TOAST classifications have been introduced since the start of the SLSR in 1995, therefore, as part of the medical notes review, I classified both the initial and first recurrence stroke event according to the OCSP and TOAST criteria. These classifications were then verified with a senior stroke physician. Both the OCSP and TOAST classifications have previously been validated to be applied retrospectively as well as for prospective use[15].

- Finally, in order to ensure that all possible cases of stroke recurrence were included known to the SLSR and therefore included in the analyses, I undertook a review of the data sent to the SLSR from the Office of National

Statistics (ONS). The ONS sent quarterly data to the SLSR stating the cause of death of patients registered with the SLSR since 1995. I designed, and having conducted a pilot study to check sensitivity, applied an algorithm (Appendix 3) using the ICD-9 or ICD-10 codes (International classification of diseases, 9th revision or 10th revision) to identify any further patients who may have had a stroke recurrence prior to death. The notes of these patients were then reviewed in order to ascertain clinically whether a further stroke had occurred, and if appropriate the stroke recurrence is registered.

These measures outlined above contributed towards the development of a an updated dataset which was used to conduct the analyses described in Chapters 5 and 6 of this thesis.

2.6 Search strategies used for systematic review of the literature

A comprehensive search of the literature was conducted using Ovid Medline (1950-December 2009), EMBASE (1950-December 2009) and the Web of Science. These databases were searched by use of both the medical subject heading (MESH) terms and free text, combining terms for stroke (stroke OR cerebrovascular disease OR cerebrovascular accident) AND stroke recurrence (recurren*).

In addition, the reference lists of all identified studies and the contents pages of relevant peer-reviewed journals, as well as abstracts from national and international conferences related to stroke were hand-searched in order to identify studies not previously identified by the electronic searches. All searches included studies published up to the end of December 2009. These literature searches were updated to include articles published before January 11th 2014 for the purposes of this thesis.

2.7 Statistical methods

2.7.1 Survival analysis

Survival analysis is the method for analysing data where the outcome variable is the time until the occurrence of an event of interest. It is otherwise known as 'time-to-event analysis'. The event can be death or the occurrence of a disease, and can be measured in days or weeks or even hours[86].

Observations are censored when information about survival time are incomplete, for example if subjects do not experience the event during the follow-up period; if they die prior to the end of the study (provided the study is not estimating the time to death); or if they drop out of the study before the end of the study period.

Survival methods incorporate information from both censored and uncensored observations in estimating important model parameters. The dependent variable in survival analysis is composed of two parts: one is the time to event and the other is the event status, which records if the event of interest occurred or not. Two functions which are dependent on time (the survival and hazard functions) can then be estimated. The survival and hazard functions are key concepts in survival analysis for describing the distribution of event times. The survival function gives, for every time, the probability of surviving (or not experiencing the event) up to that time. The hazard function gives the potential that the event will occur, per time unit, given that an individual has survived up to the specified time.

A number of models are available to analyse the relationship of a set of predictor variables with the survival time. Methods include parametric, nonparametric and semi-parametric approaches[87].

Parametric methods assume that the underlying distribution of the survival times follows a known probability distribution such as the exponential, Weibull, and

lognormal distributions. The distribution of survival times and changes in the distribution due to the addition of covariates or predictors are analysed. Model parameters in these settings are usually estimated using an appropriate estimation of maximum likelihood, that is, by estimating the value which makes the observed values most probable.

A nonparametric estimator of the survival function, the Kaplan Meier method is widely used to estimate and graph survival probabilities as a function of time and in particular to obtain univariate descriptive statistics for survival data. To test for overall differences between estimated survival curves of two or more groups of subjects, the log-rank test can be used to compare the Kaplan-Meier curves estimated for each group of subjects.

The semi-parametric Cox proportional hazards regression model is used to test for differences in survival times of two or more groups of interest, while allowing adjustment for covariates of interest.

The Cox model describes the relation between the event incidence, as expressed by the hazard function and a set of covariates and which mathematically is written as:

$$h(t) = h_0 (t) \times \exp \{b_1x_1 + b_2x_2 + ... + b_px_p\}$$

where the hazard function h(t) is dependent on (or determined by) a set of p covariates (x_1, x_2, ... x_p), whose impact is measured by the size of the respective coefficients (b_1, b_2 ... b_p). The term h_0 is called the baseline hazard, and is the value of the hazard if all the x_i are equal to zero. The 't' in h(t) indicates that the hazard may (and probably will) vary over time.

While a non-linear relationship between the hazard function and the predictors is assumed, the hazard ratio comparing any two observations is constant over time

in the setting where the predictor variables do not vary over time. This assumption is called the proportional hazards assumption and checking if this assumption is met is an important part of a Cox regression analysis[87].

The proportional hazards assumption can be checked by plotting the Kaplan–Meier survival curves together. If they cross, then the proportional hazards assumption may be violated. However, for small data sets, the survival curves may cross even under the proportional hazards assumption, and a log-log plot may be conducted. This plot will display parallel curves if hazards are proportional across the groups[88].

If the proportional hazards assumption is not met in a model, several techniques can be used. These include stratification by the categories of the variable for which the assumption fails; the use of separate Cox models for different time intervals; or the use of time-dependent covariates[89].

2.7.2 Statistical methods used in this thesis

This thesis uses survival analyses to investigate the time to stroke recurrence and time to death after first-ever stroke. The analyses conducted in this thesis have been performed using a combination of 'SPSS', 'STATA' and 'SAS' statistical packages. Specific analyses have been undertaken to address the research objectives outlined in Section 1.9 of this thesis:

- *Can we estimate the risk of stroke recurrence at different time-points up to 12 years after first-ever stroke?*

The survival probability will be estimated non-parametrically from observed survival times, both censored and uncensored, using the Kaplan-Meier (or

product-limit) method. Patients will be censored at time of death, lost to follow-up, or if alive at the end of the follow-up period.

Kaplan-Meier estimates will be calculated to model the risk of stroke recurrence (1-survival free of recurrent stroke) and therefore to measure the cumulative risk of stroke recurrence and 95% confidence intervals up to 12 years after initial stroke. Finally, a meta-regression model will be used to derive parameter estimates of cumulative risk as a function of time since first stroke, allowing comparisons to be made at time-points not analysed during the study.

- *Is it possible to identify factors which predict the risk of stroke recurrence, from variables including socio-demographic factors, risk factors diagnosed at the time of initial stroke, patterns in stroke subtype classifications, and stroke severity markers, at different time-points up to 12 years after first-ever stroke?*

Hazard ratios (HR) and the corresponding 95% confidence intervals (CI) will be estimated using Cox regression analyses and the assumption of proportional hazards will be assessed using log minus log survival plots.

Again, patients will be censored at time of death (if not due to stroke recurrence), if lost to follow-up, or if alive at the end of the follow-up period. In the multivariable analyses, the influence of socio-demographic factors, stroke severity, cardiovascular risk factors and stroke subtypes shall be investigated as potential predictors of stroke recurrence and results shall also be stratified by pathological and aetiological stroke subtype.

Can effective management of stroke, and the appropriate use of secondary prevention medication at the appropriate time-point after initial stroke reduce the risk of stroke recurrence?

In order to estimate the effect of secondary prevention medication on the risk of stroke recurrence at any time point after first stroke time-dependent (or updated) covariate methods shall be used to fit a multi-level time-dependent predictive model. This will allow variables which may not have been part of the baseline assessment at time of first stroke to be included in the survival model. Therefore, the effect of secondary prevention medication, for example, anti-hypertensive therapy or anticoagulation with warfarin can be estimated within the analyses, regardless of at which time-point the medication is started. For example, for the Cox Regression model previously described, the formula relating a covariate x_1 to the hazard h(t) is

$$h(t) = h_0(t)\, exp[b_1 x_1]$$

where $h_0(t)$ is the baseline hazard. If repeated measurements of a covariate x_1 are available, this formula will change to

$$h(t) = h_0(t)\, exp[b_1 x_1(t)]$$

where $x_1(t)$ is the value of x_1 at time *t.* The coefficient b_1 represents the additional relative hazard for each unit increase in x_1 at any given time.

- *Does stroke recurrence have an effect on the risk of death after first stroke?*

Kaplan-Meier estimates will be calculated to model the risk of death (1-survival) and therefore to measure the cumulative risk of death using Hazard Ratios (HR) and corresponding 95% confidence intervals up to 15 years after first stroke.

In the multivariable analyses, stratified Cox Proportional Hazards Models will be used to estimate the effect of stroke recurrence on the risk of death after first stroke adjusted for socio-demographic factors, stroke severity, cardiovascular risk factors, stroke subtypes, process of care variables, and time- dependent factors. Stroke recurrence will be treated as a time-varying covariate in the analyses, using STATA to split the dataset at time of stroke recurrence, to adjust for the

eventuality that an individual may die from a non-related cause before stroke recurrence, therefore not allowing a stroke recurrence to occur.

The specifics of the methods used to fulfil these objectives shall be discussed in further detail in the relevant chapters of this thesis.

2.8 Summary

This chapter presented the rationale for the use of the SLSR as a sampling frame for this thesis, as well as the general methods used in both the literature searches and statistical analyses presented in the rest of the thesis.

As a starting point for the exploration of this thesis, the next chapter outlines the preliminary studies conducted to identify whether modifiable risk factors are important in predicting stroke recurrence within the SLSR population. These preliminary analyses also provide an opportunity to assess the SLSR dataset and to highlight any limitations to be addressed prior to conducting further analyses.

Chapter 3. Frequency and predictors of stroke recurrence

The description of the risk and predictors of, stroke recurrence up to 10 years after first stroke was presented as an oral presentation at the World Stroke Congress in 2008 and has been published as an original research paper in the Journal of Neurology, Neurosurgery and Psychiatry in 2009. (See Appendix 1).

Abstract

Background- Data estimating the risk of, and predictors for long-term stroke recurrence are lacking.

Methods- Data were collected from the population-based South London Stroke Register. Patients were followed up until March 2008 or for a maximum of 10 years after first stroke. Kaplan-Meier estimates and Cox Proportional Hazards models were used to assess cumulative risk of and predictors for first stroke recurrence. Variables analysed included socio-demographic factors, stroke subtype (defined as cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage), stroke severity markers and prior-to-stroke risk factors.

Results- Between 1995 and 2004, 2874 patients with first-ever stroke were included. Mean follow-up period was 2.9 years. During 8311 person-years of follow up, 303 recurrent events occurred. The cumulative risk of stroke recurrence at 1 year, 5 years and 10 years was 7.1%, 16.2% and 24.5% respectively. No differences in stroke recurrence were noted between the stroke subtypes. Factors increasing the risk of recurrence at 1 year, were previous myocardial infarction (HR 1.73; 95% CI 1.08-2.78) and atrial fibrillation (HR 1.61; 95% CI 1.04-4.27); at 5 years, hypertension (HR 1.47; 95% CI 1.08-1.99) and atrial fibrillation (HR 1.79; 95% CI 1.29-2.49); and at 10 years, older age (p=0.04), and hypertension (HR 1.38, 95% CI 1.04-1.82), myocardial infarction (HR 1.50, 95% CI 1.06-2.11), and atrial fibrillation (HR 1.51, 95% CI 1.09-2.09).

Conclusions-Very long-term risk of stroke recurrence is substantial. Some variation in predictors for stroke recurrence were noted, however baseline

cardiovascular risk factors were found to have a significant role in predicting stroke recurrence at all time-points up to 10 years.

3.1 Introduction

Predictors of stroke recurrence remain largely unknown with socio-demographic factors, co-morbidities and stroke subtype outlined as important in different studies[17, 90, 91]. The aim of this study was to estimate the risk and predictors of first stroke recurrence up to 10 years after initial stroke within a population-based setting.

This is important as it was hypothesised that the treatment of modifiable predictors of stroke recurrence, at the appropriate time point after stroke recurrence reduces the risk of stroke recurrence. In order for this to be clinically as well as statistically relevant, modifiable risk factors need to convey increased risk of stroke recurrence within the population.

The analyses presented in this chapter were conducted using data related to first-ever strokes recorded prospectively for the South London Stroke Register from 1995 to 2004. Whilst the use of a long-term sampling frame will undoubtedly be a strength of this study, these preliminary studies also provide an opportunity to assess the dataset and methods to be used, identify any gaps in the data collected, and investigate possible methods to reduce missing data later in this thesis.

3.2 Methods

The use of the South London Stroke Register as the study population, the case ascertainment and data collection methods used in this chapter have previously been discussed in Chapter 2 of this thesis.

3.2.1 Variable definition

Stroke was defined according to the World Health Organisation (WHO) criteria[81]. The pathological subtype of stroke was classified as cerebral

infarction (CI), primary intracerebral haemorrhage (PICH), subarachnoid haemorrhage (SAH) or undefined (UND). Classification was based on results from at least one of the following: brain imaging performed within 30 days of stroke (computerised tomography or magnetic resonance imaging), analysis of cerebrospinal fluid (in all living patients with subarachnoid haemorrhage in whom brain imaging was not diagnostic) or necropsy examination.

3.2.1.1 Definition of stroke recurrence

The definition of stroke recurrence was the same as for the index stroke. Additionally, clinical diagnosis of a new neurological deficit, or deterioration of a previous deficit not due to oedema, haemorrhagic transformation, or inter-current illness was required. Only recurrences 21 days after the initial event, or if earlier, clearly in a different vascular territory were included. The same referral sources were used for notification of stroke recurrences as for initial stroke ascertainment. All patients were eligible for follow-up if alive and having reached the specified point of follow-up by March 2008.

As potential predictors of stroke recurrence, the following variables were selected. Demographic factors included age (categorised as <65, 65-74, ≥75), gender, ethnicity (categorised as white, black and other) and socio-economic status. Socioeconomic status categories were grouped into non-manual (I, II, and III non-manual) or manual (III manual, IV, and V) according to the patient's current (or for the retired and others not currently working, the most recent) employment. Co-morbidities included history of transient ischaemic attack (TIA), ischaemic heart disease, atrial fibrillation (AF), hypertension, diabetes mellitus and smoking. Smoking status was recorded as current smoker or non- or ex-smoker.

Stroke severity was defined as the maximum neurological deficit recorded during the acute phase, or first 14 days, after the initial stroke. Case severity variables included motor deficit, urinary incontinence, and Glasgow coma scale (categorised as 3-8, 9-12, 13-15)[92].

3.2.2 Statistical analyses

Descriptive and univariate analyses using Kaplan-Meier estimates were used to model the risk of recurrent stroke (1- survival free of recurrent stroke) and therefore to measure the cumulative risk of stroke recurrence and 95% confidence intervals (CI) at 1, 5 and 10 years post initial stroke. For each variable individually, hazard ratios (HR) and the corresponding 95% confidence intervals (CI) were estimated using Cox regression analyses. The assumption of proportional hazards was assessed using log minus log survival plots. Patients were censored at time of death, or if alive at 10 years after stroke.

In the multivariable analyses, the influence of demographics, pathological subtype of the initial event, stroke severity, and co-morbidities as predictors of stroke recurrence were investigated. When analysing age, the broad ≥75 category was used due to the small numbers of patients surviving to long term follow up who were in higher age groups. Variables included in the multivariable analyses were eliminated using the backward elimination procedure. In the backward elimination procedure all covariates were entered into the Cox model in the first step. With each proceeding step, the covariate showing the smallest contribution to the model is removed until just covariates which have a significant effect on the Cox model remain. As covariates were removed from the model at different steps, the multivariable analyses presented in Table 8 report hazard ratios and the significance level immediately prior to each covariate leaving the model.

Possible interactions between age, stroke subtype and co-morbidities were controlled by adding terms of interaction to the regression model. Multivariable analyses were restricted to patients without missing values which totalled 2268 patients. The number of patients with missing values ranged from 0 for the age, gender and stroke subtype variables, to 254 (8.8%) for incontinence at time of initial stroke.

A sensitivity analysis was performed with patients censored at time of follow-up rather than at date of death, if death occurred more than 1 year after last follow-up.

Further sensitivity analyses were performed as requested as part of amendments to this thesis. Multiple imputation was performed to impute all missing baseline covariates. All baseline variables were included as well as the log of survival time and the recurrence indicator. Fully conditional specification method was used meaning that each variable with missing data were imputed one at a time using all the other variables. 20 imputations were carried out[93]. Cox models were fitted within imputed dataset and parameter estimates were combined using Rubin's rules[94]. All variables were entered into the Cox Models in a single step.

As the multivariable analyses presented estimate the cumulative risk of recurrence sensitivity analyses were also carried out to assess the associations between recurrence and baseline characteristics between defined specific time periods of 1 to 5 years and 5 to 10 years after initial stroke. Due to the small numbers of recurrences occurring in the 5 to 10 year period, variables included in these analyses were eliminated using the forward elimination procedure.

All tests were two-tailed and p values <0.05 were regarded as statistically significant. Statistical analyses were performed using SPSS version 16.1 and STATA software version 10(SE).

3.3 Results

This study included a total of 2874 first-ever stroke patients registered between January 1995 and December 2004. The mean follow-up time was 2.9 years, with a median time of 1.93 years and a total of 8310.5 person years of follow-up

included. During this period, 303 recurrent strokes were documented. Patient characteristics at time of initial stroke are presented in Table 5.

The number of patients in the study at the different key time-points during the 10 year study period are summarised in Table 6. The number participants remaining in the study throughout the study period by covariate, can be found in Appendix 6.

	Total, N(%)
Total	2874
Age group	
<65	863(30)
65-74	764(27)
75-84	1247(43)
Gender	
Female	1447(50)
Ethnicity	
White	2126(76)
Black	525(19)
Other	153(5.5)
Socio economic status	
Non-manual	730(25)
Manual	1604(56)
Unknown	540(19)
Stroke Subtype	
Infarct	2089(73)
PICH	395(14)
SAH	171(6.0)
Undefined	219(7.6)
Risk factors	
Previous TIA	358(13)
Hypertension	1714(64)
Diabetes Mellitus	483(18)
Previous MI	315(12)
Previous AF	463(17)
Smoker or ex-smoker	943 (36)
Stroke severity Indices	
GCS ≤8	497(18)
9-12	422(15)
13-15	1835(67)
Motor deficit	2282(84)
Incontinence	1238(47)

Table 5.Descriptive baseline statistics

Abbreviations: PICH Primary Intracerebral Haemorrhage, SAH Subarachnoid Haemorrhage

Time after first stroke	Number at start of time period	Number with stroke recurrence	Number censored - died	Number censored – end of time-period	Number in study at end of time-period
0-1 years	2874	142	1042	65	1625
1- 5 years	1625	122	440	345	718
5-10 years	718	39	203	391	85

Table 6. The number of participants in the study throughout the study period.

3.3.1 Survival Analyses

The cumulative risk of first stroke recurrence at 1 year, 5 years and 10 years was 7.1% (95% CI 6.0 to 8.3%), 16.2% (95% CI 14.4 to 18.1%) and 24.5% (95% CI 21.3 to 27.9%) respectively. Table 7 shows the univariate analyses of cumulative risk of stroke recurrence up to 10 years.

	Cumulative risk of recurrence, % (95% CI)		
	At 1 year	At 5 years	At 10 years
Total	7.1 (6.0-8.3)	16.2 (14.4-18.1)	24.5 (21.3 – 27.9)
Age group			
<65	6.2 (4.6-8.3)	12.6 (10.1-15.6)	17.2 (13.8-21.4)
65-74	6.6 (4.8-9.0)	16.2 (13.1-20.0)	29.6 (23.4-36.8)
≥75	8.4 (6.6-10.6)	20.4 (17.0-24.5)	30.1 (21.3-41.4)
Gender			
Male	6.0 (4.7-7.6)	15.5 (13.1-18.2)	22.9 (19.1-27.4)
Female	8.4 (6.8-10.4)	17.1 (14.4-20.1)	26.4 (21.5-32.2)
Ethnicity			
White	7.4 (6.2-8.9)	16.1 (14.0-18.5)	25.1 (21.2-29.5)
Black	6.1 (4.1-8.8)	16.7 (13.0-21.3)	23.7 (18.4-30.2)
Other	7.7 (4.1-14.2)	15.7 (9.7-24.6)	20.8 (12.9-32.6)
Socio economic status			
Non-manual	6.5 (4.7-8.8)	14.7 (11.7-18.3)	26.3 (20.6-33.3)
Manual	7.7 (6.3-9.3)	17.5 (15.1-20.2)	24.9 (21.0-29.3)
Unknown	5.9 (3.2-11.0)	14.5 (9.3-22.3)	17.0 (10.6-26.5)
Stroke Subtype			
Infarct	6.9 (5.8-8.3)	16.6 (14.6-18.9)	25.7 (21.9-29.9)
PICH	7.7 (4.8-12.2)	16.5 (11.6-23.1)	19.5 (13.6-27.6)
SAH	4.7 (2.0-11.0)	4.7 (2.0-11.0)	7.5 (3.0-17.9)
Undefined	11.9 (6.5-21.2)	21.6 (13.6-33.3)	43.4 (25.5-66.8)
Risk factors			
No TIA	7.0 (5.9-8.4)	15.4 (13.4-17.6)	24.9 (21.4-28.8)
Previous TIA	9.5 (6.5-13.7)	22.0 (16.9-28.5)	26.5 (19.0-36.1)
No Hypertension	6.6 (4.9-8.8)	12.6 (10.0-15.8)	18.7 (14.7-23.7)
Hypertension	7,8 (6.4-9.5)	18.4 (16.0-21.1)	27.8 (23.6-32.5)
No Diabetes Mellitus	7.2 (6.0-8.6)	15.6 (13.6-18.0)	23.8 (22.2-41.3)
Diabetes Mellitus	8.4 (5.9-11.9)	20.0 (15.6-25.3)	30.6 (22.2-41.3)
No MI	6.9 (5.8-8.3)	15.7 (13.7-17.8)	23.4 (20.1-27.1)
Previous MI	11/3 (7.7-16.6)	22.6 (16.6-30.3)	41.1 (29.1-55.8)
No AF	6.9 (5.8-8.3)	15.4 (13.5-17.5)	24.6 (21.2-28.5)
Previous AF	9.9 (6.8-14.3)	24.7 (18.6-32.4)	27.5 (20.0-37.1)
Non-Smoker	8.1 (6.7-9.8)	17.5 (15.1-20.1)	26.4 (21.8-31.6)
Smoker or ex-smoker	5.4 (4.0-7.4)	13.9 (11.2-17.1)	21.0 (17.1-25.6)
Stroke severity Indices			
GCS ≤8	3.2 (1.1-9.2)	10.1 (4.7-20.9)	10.1 (4.7-20.9)
9-12	7.7 (4.9-11.9)	13.8 (9.5-19.9)	18.1 (11.6-27.4)
13-15	7.2 (6.1-8.6)	16.4 (14.4-18.6)	25.4 (21.8-29.4)
No motor deficit	6.1 (4.1-9.1)	16.0 (12.3-20.6)	22.5 (15.6-31.8)
Motor deficit	7.4 (6.2-8.8)	16.3 (14.3-18.6)	25.1 (21.7-29.0)
No incontinence	6.4 (5.2-7.9)	15.6 (13.4-18.0)	24.9 (20.9-29.3)
Incontinence	8.1 (6.2-10.6)	15.6 (12.4-19.5)	21.0 (16.3-26.8)

Table 7. Univariate analyses: cumulative risk of stroke recurrence

Figure 2 shows a Kaplan-Meier plot graphically representing the risk of stroke recurrence (1-survival free of recurrent stroke) over 10 years stratified for stroke subtype.

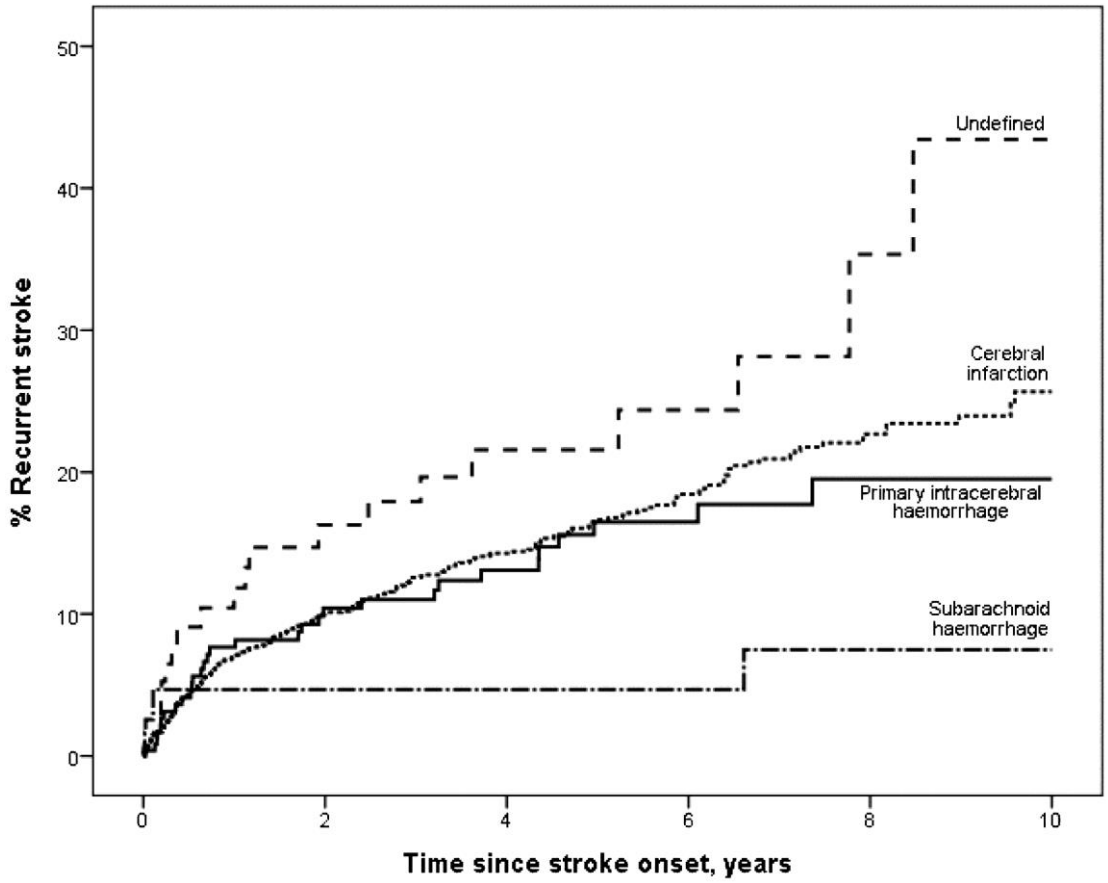

Figure 2. Cumulative risk of stroke recurrence stratified according to stroke subtype.

The multivariable analyses for predictors of cumulative risk of stroke recurrence up to 1 year, 5 years and 10 year after first stroke, are shown in Table 8. Log-log plots were conducted to show that the proportional hazards assumption was fulfilled across all variables included in the model and can be found in Appendix 4.

Up to 1 year post-stroke, a past history of myocardial infarction and atrial fibrillation were found to be predictors of early stroke recurrence, whilst gender demonstrated borderline significance. Up to 5 years, prior-to-stroke hypertension

and atrial fibrillation were found to be predictors, with previous myocardial infarction demonstrating borderline significance; and up to 10 years, older age and a history of hypertension, myocardial infarction and atrial fibrillation diagnosed prior to first stroke, were found to be predictors of long-term stroke recurrence. However it is notable that for each covariate, the confidence intervals estimated throughout the 10 year time-period overlap, indicating that, for example, the cardiovascular risk factors identified as predictors in specific analyses are likely to predict the increased risk of stroke recurrence throughout the 10 year time-period.

In the sensitivity analyses, no significant differences in cumulative risk of recurrence were observed if patients were censored at time of follow-up rather than at date of death, if death occurred more than 1 year after last follow-up. Furthermore, in the multivariable analyses the predictors of recurrence remained the same while hazard ratios and corresponding confidence intervals were stable. None of the interactions tested were found to be significant except between stroke subtype at 10 years and a history of previous TIA at 10 years. There was a higher risk of recurrent stroke experienced by SAH patients who had had a previous TIA. However, this interaction was based on a very small number of patients who had a SAH and therefore the results were not reported stratified.

Sensitivity analyses were also conducted using multiple imputation to impute all missing baseline covariates into the multivariable analyses. The hazard ratios estimated using the imputed dataset are presented in Table 9. Due to the multiple imputation method used, p values have not been reported across the categorical variables.

It is notable that the hazard ratios and confidence intervals estimated using the imputed dataset are similar to those estimated in the original analyses, with cardiovascular risk factors remaining important across the time period. Certain differences can be noted, for example hypertension was no longer statistically

significant after multiple imputation. In the period up to 5 years after first stroke, the 95% Confidence Intervals estimated became wider when multiple imputation methods were used increasing from HR 1.47 (1.08-1.99) to HR 1.20 (95% CI 0.90-1.59).

As outlined in earlier in this chapter, these sensitivity analyses were performed with all variables entered into the Cox models in the same step, rather than by the backwards elimination method used in the main analyses which is likely to lead to slight variation in results. Furthermore, it has been previously commented that the fully conditional specification method of multiple imputation can lead to Type 2 errors, leading to an under-estimation of hazard ratios obtained by this method[95]. For these reasons, and as the hazard ratios and confidence intervals estimated using these multiple imputation methods, are similar to those presented in the main analyses of this chapter (Table 8), sensitivity analyses using multiple imputation methods have not been performed in the remaining analyses in this thesis.

Further sensitivity analyses were carried out to assess differences between the method of estimating cumulative risk of stroke recurrence (i.e. up to 5 years, and up to 10 years after first stroke) taken in the analyses of this thesis, compared to using defined specific time periods of 1 to 5 years and 5 to 10 years. In the 1 to 5 year period, hypertension (HR 2.07 (95%CI 1.22-3.50); p<0.01) and atrial fibrillation (HR1.84 (95%CI 1.09-3.12) were found to be predictors of stroke recurrence. In the 5 to 10 year period, older age (age 65-74 (HR 4.13 95% CI 1.64-10.4) and age 75< (HR 2.98 95% CI 1.03-8.61) when compared to age <65 (overall p value 0.01)) and past history of a myocardial infarction (HR 2.49 95% CI 1.08-5.77) were identified to increase the risk of stroke recurrence. It should be noted that forwards elimination methods were used to estimate the predictors of stroke recurrence in the 5 to 10 year period due to the small numbers involved. The merits of estimating the cumulative risk of stroke recurrence compared to using this method shall be discussed later in this chapter.

	1 Year		5 Year		10 Year	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95% CI)	P value
Age group						
<65	1	0.79	1	0.14	1	0.04†
65-74	0.90 (0.55-4.62)		1.10 (0.77-1.57)		1.36 (0.98-1.87)	
≥75	1.05 (0.63-5.17)		1.37 (0.99-1.91)		1.50 (1.10-2.05)	
Gender						
Male	1	0.07†	1	0.58	1	0.48
Female	1.40 (0.98-2.00)		1.08 (0.82-1.42)		1.09 (0.85-1.41)	
Ethnicity						
White	1	0.90	1	0.52	1	0.60
Black	0.90 (0.55-1.48)		1.20 (0.85-1.68)		1.17 (0.85-1.62)	
Other	1.06 (0.48-2.35)		1.22 (0.69-2.15)		1.15 (0.66-1.98)	
Socio economic status						
Non-manual	1	0.29	1	0.66	1	0.71
Manual	1.25 (0.82-1.90)		1.11 (0.81-1.51)		1.01 (0.76-1.34)	
Unknown	0.97 (0.44-2.12)		0.89 (0.49-1.63)		0.80 (0.48-1.43)	
Stroke Subtype						
Infarct	1	0.72	1	0.51	1	0.53
PICH	1.29 (0.73-2.26)		1.11 (0.74-1.69)		0.99 (0.66-1.48)	
SAH	1.05 (0.31-3.57)		0.44 (0.14-1.40)		0.47 (0.17-1.28)	
Undefined	1.42 (0.62-3.27)		1.00 (0.49-2.03)		1.01 (0.54-1.91)	
Risk factors						
No TIA	1	0.68	1	0.19	1	0.61
Previous TIA	1.11 (0.69-1.78)		1.26 (0.89-1.78)		1.09 (0.78-1.52)	
No Hypertension	1	0.56	1	0.01†	1	0.03†
Hypertension	1.12 (0.76-1.65)		1.47 (1.08-1.99)		1.38 (1.04-1.82)	
No Diabetes Mellitus	1	0.79	1	0.10	1	0.14
Diabetes Mellitus	1.06 (0.68-1.68)		1.31 (0.95-1.81)		1.26 (0.93-1.71)	
No MI	1	0.02†	1	0.09†	1	0.02†
Previous MI	1.73 (1.08-2.78)		1.39 (0.95-2.03)		1.50 (1.06-2.11)	
No AF	1	0.03†	1	<0.01†	1	0.01†
Previous AF	1.61 (1.04-2.47)		1.79 (1.29-2.49)		1.51 (1.09-2.09)	
Non-Smoker	1	0.61	1	0.55	1	0.46
Smoker or ex-smoker	0.90 (0.60-1.35)		1.10 (0.81-1.50)		1.11 (0.84-1.48)	
Stroke severity Indices						
GCS ≤8	1	0.56	1	0.61	1	0.63
9-12	1.48 (0.49-4.46)		0.99 (0.44-2.23)		1.01 (0.45-2.24)	
13-15	1.71 (0.61-4.84)		1.23 (0.58-2.62)		1.21 (0.59-2.48)	
No motor deficit	1	0.16	1	0.60	1	0.89
Motor deficit	1.46 (0.86-2.47)		0.91 (0.64-1.30)		0.98 (0.70-1.37)	
No incontinence	1	0.52	1	0.72	1	0.54
Incontinence	1.13 (0.78-1.65)		1.06 (0.79-1.42)		1.10 (0.82-1.48)	

Table 8. Multivariable analyses: cumulative risk of stroke recurrence at 1, 5, and 10 years*

Abbreviations: CI confidence interval PICH Primary Intracerebral Haemorrhage, SAH Subarachnoid Haemorrhage

*Analyses restricted to patients without missing values †Variables included in the final model ($p<0.10$). All other values recorded immediately prior to removal from the model by the backward elimination procedure.

	HR (95%CI)	P value	HR (95%CI)	P value	HR (95% CI)	P value
Age group						
<65	1		1		1	
65-74	0.84(0.53-1.33)	0.45	1.08(0.77-1.50)	0.67	1.25 (0.92-1.69)	0.15
≥75	0.98(0.63-1.54)	0.93	1.40 (1.00-1.95)	0.05	1.48 (1.08-2.02)	0.01
Gender						
Male	1		1		1	
Female	1.34(0.95-1.90)	0.10	1.08 (0.84-1.39)	0.57	1.08 (0.86-1.37)	0.51
Ethnicity						
White	1		1		1	
Black	0.83 (0.52-1.33)	0.43	1.13 (0.82-1.57)	0.45	1.13 (0.84-1.54)	0.42
Other	1.11 (0.55-2.25)	0.77	1.20 (0.70-2.03)	0.51	1.15 (0.70-1.90)	0.58
Socio economic status						
Non-manual	1		1		1	
Manual	1.14 (0.77-1.67)	0.52	1.11 (0.84-1.48)	0.46	1.00 (0.77-1.30)	0.99
Stroke Subtype						
Infarct	1		1		1	
PICH	1.24 (0.72-2.13)	0.45	1.12 (0.75-1.69)	0.57	1/03 (0.70-1.51)	0..90
SAH	1.23 (0.46-3.30)	0.69	0.54 (0.21-1.38)	0.20	0.55 (0.23-1.29)	0.17
Undefined	1.94 (1.01-3.73)	0.05	1.61 (0.96-2.69)	0.07	1.69 (1.07-2.68)	0.03
Risk factors						
No TIA	1		1		1	
Previous TIA	1.34 (0.87-2.08)	0.19	1.40 (1.02-1.92)	0.04	1.21 (0.89-1.65)	0.22
No Hypertension	1		1		1	
Hypertension	1.04 (0.72-1.51)	0.83	1.20 (0.90-1.59)	0.21	1.20 (0.92-1.56)	0.18
No Diabetes Mellitus	1		1		1	
Diabetes Mellitus	1.21 (0.79-1.86)	0.38	1.29 (0.95-1.75)	0.11	1.24 (0.93-1.67)	0.15
No MI	1		1		1	
Previous MI	1.69 (1.08-2.66)	0.02	1.48 (1.11-2.16)	0.03	1.57 (1.13-2.17)	<0.01
No AF	1		1		1	
Previous AF	1.35 (0.87-2.11)	0.19	1.55 (1.29-2.49)	0.01	1.37 (0.98-1.92)	0.06
Non-Smoker	1		1		1	
Smoker or ex-smoker	0.76 (0.50-1.16)	0.20	0.97 (0.73-1.30)	0.85	0.99 (0.76-1.30)	0.96
Stroke severity Indices						
GCS ≤8	1		1		1	
9-12	2.09 (0.68-6.39)	0.20	1.34 (0.60-3.01)	0.47	1.44 (0.66-3.15)	0.36
13-15	2.30 (0.80-6.63)	0.13	1.57 (0.74-3.34)	0.24	1.73 (0.82-3.63)	0.15
No motor deficit	1		1		1	
Motor deficit	1.15 (0.71-1.86)	0.58	0.87 (0.64-1.21)	0.43	0.98 (0.72-1.33)	0.91
No incontinence	1		1		1	
Incontinence	1.27 (0.85-1.90)	0.25	1.13 (0.82-1.54)	0.46	1.09 (0.82-1.46)	0.55

Table 9. Multivariable analyses: cumulative risk of stroke recurrence at 1, 5, and 10 years using multiple imputation to estimate missing baseline covariates

Abbreviations: CI confidence interval PICH Primary Intracerebral Haemorrhage, SAH Subarachnoid Haemorrhage

3.4 Discussion

This study estimated the risk of and predictors for stroke recurrence up to 10 years after initial stroke. The results show that the cumulative risk of first stroke recurrence is substantial (i.e.) up to 25% by 10 years post-initial stroke, and also identifies predictors of stroke recurrence up to 1, 5 and 10 years after first stroke. No independent influence of stroke subtype or stroke severity on stroke recurrence up to 10 years was identified and no differences between ethnic or socio-economic groups were revealed. Prior-to-stroke risk factors were found to have a significant role in predicting stroke recurrence up to 10 years.

The mean follow-up period for this study was 2.9 years. This may initially appear low however as demonstrated in Table 6, 1042 out of 2874 study participants (36.3%) died within the first year of this study. The risk of death after first stroke is known to vary widely between published estimates, and the impact of stroke recurrence on death after first stroke will be considered further in Chapter 7 of this thesis.

The results estimated no significant differences between ischaemic and haemorrhagic stroke subtypes up to 1, 5 and 10 years post-stroke. This contrasts with research from Japan that found the risk of stroke recurrence to be significantly greater within 1 year of an initial ischaemic stroke compared with haemorrhagic stroke. However, these differences were not maintained beyond 1 year, and there were no significant differences noted during the rest of their follow-up period of 3 years[96]. Conversely, The Perth Community Stroke Study reported prognostic factors for recurrent stroke at 5 years including advanced age and an initial stroke subtype of either PICH or SAH, which achieved borderline significance in their analyses[97].

This study found no differences between markers of stroke severity as predictors of stroke recurrence at any time point. Baseline results from the African-American Antiplatelet Stroke Prevention Study (AAAPS) found that stroke severity and disability at the time of initial event, were significantly associated with increases in stroke recurrence

in black patients during 2 years of follow-up[98]. The association between severity of first stroke and stroke recurrence is undoubtedly complex, as increased first stroke severity may mask the identification of stroke recurrence. The impact of stroke recurrence on disability after first stroke is not considered as part of this thesis, but clearly this is an area for further research, beyond this thesis, to be targeted.

Work previously described by the SLSR has shown that black patients maintain a higher initial stroke risk than white patients[14], yet the results presented in this chapter indicate that this increased risk does not confer an increased susceptibility to stroke recurrence amongst our black population. It has previously been found by both the SLSR and the Northern Manhattan Stroke Study that different risk factors and co-morbidities may be important in black and white patients[99, 100] and the SLSR has previously demonstrated increased survival after first stroke in black patients compared to white patients over 65 years[101]. This study importantly shows that these survival differences are not caused by differences in stroke recurrences between these ethnic groups.

The results presented in this chapter demonstrate the importance of management of co-morbidities and traditional vascular risk factors as predictors of recurrence At 1 year, atrial fibrillation and myocardial infarction were identified as predictors of stroke recurrence. This is also demonstrated in the FINMONICA Stroke Register, which identified myocardial infarction and atrial fibrillation to be independent predictors of recurrence at 1 year in patients ages 75 years and over[102]. Results from the Nanjing Stroke Registry showed hypertension, atrial fibrillation and smoking to be predictors at 1 year, however these results found hypertension only became a significant predictor of recurrence during later follow-up, and smoking not to be a predictor at any time-point investigated[103].

Cardiovascular risk factors such as, hypertension and atrial fibrillation were identified as predictors for stroke recurrence up to 5 years post-stroke. There is much variation in previous literature regarding predictors for stroke recurrence beyond 1 year. Diabetes

has been shown to be a predictor for recurrence beyond 1 year[97, 104], and up to 10 years in patients with a first cerebral infarction[17]. The Lehigh Valley Recurrent Stroke Study found a past history of hypertension, and a transient ischaemic attack (TIA) after initial stroke to be independent predictors for stroke recurrence up to 5 years. However, similar to our results, they also found that a history of TIA prior to initial stroke was not a predictor of stroke recurrence[105, 106].

The results demonstrate the importance of cardiovascular risk factors throughout the follow-up period, and supplement previous work identifying the impact of cardiovascular disease on long-term outcomes after first stroke[107] . In this chapter, atrial fibrillation and myocardial infarction were identified as predictors for stroke recurrence throughout the follow-up period up to 10 years.. Atrial fibrillation and myocardial infarction are known to be associated with cardio-embolic strokes which have been found to have the highest recurrence rates amongst the aetiological subtypes[108]. Hypertension, which gained importance as a predictor for stroke recurrence in the middle and long term periods, is associated with small vessel disease which has been shown to be the aetiological cause related to lacunar infarcts[20]. Therefore, patients with small vessel disease may have a lower risk of stroke recurrence in the first years after initial stroke, and may experience stroke recurrence later than other subtypes.

The plethora of prior-to-stroke risk factors identified as predictors of recurrence supports the hypothesis made in the previous chapter. The closely overlapping confidence intervals demonstrated in the analyses throughout the 10 year time period suggest that cardiovascular risk factors, in particular hypertension, atrial fibrillation and a previous history of myocardial infarction, are predictors of stroke recurrence throughout the study period. The failure to reach statistical significance might be due to Type 2 error. It seems probable that treatment of these cardiovascular risk factors, by targeted use of secondary prevention may well help to reduce stroke recurrence, or at least that it is reasonable to continue investigation as to whether this is the case.

This study had strengths and limitations. The main strengths lie in study design as by conducting a population-based study we have an unbiased sampling frame. Very long-term estimates for stroke recurrence up to 10 years after initial stroke have been provided, using standardised methods for comparability to other studies. However, discrepancies in completeness of case detection of both initial and recurrent stroke, may affect the study as patients with very mild strokes which may not present to primary or secondary care services may be missed.

Whilst the use of longitudinal data is undoubtedly a strength of this study, one of the main areas for consideration is that of missing data. It is important to ensure that the data collected is representative of the population it sets out to represent, and therefore to ensure that the maximum number of cases are included in analyses. In particular, the main multivariable analyses performed in this study, only used cases with complete data for the variables being analysed, so incomplete variables would be excluded in these analyses. Sensitivity analyses using multiple imputation methods to replace missing values were conducted as part of the amendments to this thesis. The hazard ratios and confidence intervals estimated using the imputed dataset were very similar to those presented in the main multivariate analyses of this chapter (Table 8) with similar cardiovascular predictors identified during the study period, therefore sensitivity analyses using multiple imputation methods have not been performed in the remaining analyses in this thesis

The analyses conducted in this chapter estimate the cumulative risk of stroke recurrence from initial stroke up to defined time-points (1, 5 and 10 years). An alternative way of analysing the risk of stroke recurrence would be to report risk at defined time periods i.e. 0-1, 1-5 and 5-10 years after first stroke, however this is not conventionally used in published population-based studies. Further sensitivity analyses were carried out to assess differences between the method of estimating cumulative risk of stroke recurrence (i.e. up to 5 years, and up to 10 years after first stroke) taken in the analyses of this thesis, compared to the defined specific time periods of 1 to 5 years and 5 to 10 years. It is notable that similar predictors of stroke recurrence were identified using both these methods.

Despite similar predictors of stroke recurrence being identified by both these methods, cumulative risk will be used in the remaining analyses in this thesis for three main reasons. Firstly, whilst it was possible to estimate risk of stroke recurrence up to 10 years using defined time-periods, different methods needed to be used in the 5 to 10 year period due to the small numbers involved. The use of different methods at different time-points makes longitudinal comparability difficult across the study period.

Secondly, it is important for estimates to be compared with other published population-based and hospital-based studies. A review of literature recorded on the Medline database was undertaken to identify methods used to estimate the risk of recurrence after first stroke in population-based and hospital-based studies in the two year period from 1 August 2013 to 29 August 2015. The following search terms: (stroke OR cerebrovascular disease OR cerebrovascular accident) AND stroke recurrence (recurren*) were used. Whilst these terms were the same as the terms used in the systematic review and meta-analyses in Chapter 4 of this thesis, many of the studies identified relate to a subset of stroke patients e.g. those with a diagnosis of atrial fibrillation only and therefore were not suitable for inclusion in the meta-analyses.

1976 studies were identified by the search terms and reviewed by hand, 15 studies estimated risk of recurrence after first stroke, of which 14 studies estimated the cumulative risk of recurrence (Table 10) compared to one study estimating the risk of recurrence over defined time periods (0 to 1 day; 1 to 7 days; >7days) (Table 11). The use of cumulative estimates of stroke recurrence risk in the analyses in this thesis allows comparisons to be made with other published literature, whereas use of defined time-periods were not found to be commonly used in published stroke epidemiological studies.

Study authors	Statistical methods used in analyses
Li *et al [109]*	Kaplan-Meier used to estimate the cumulative risks of outcomes including first recurrent stroke and first recurrent ischaemic stroke, up to 1-year, 5-years and 10-years after first stroke.
Yaghi *et al [110]*	Cox proportional hazard models to calculate the hazard ratios and 95% confidence intervals for total recurrent ischemic stroke up to 5 years after first stroke
Park and Ovbiagele [111]	Cox proportional hazard regression analyses were performed to estimate the risk of outcome events up to 2 years after stroke.
Zhang et al [112]	Cox regression was used to identify risk factors associated with recurrent ischemic stroke or TIA up to 1 years after stroke onset.
Lee et al [113]	Cumulative event rates as a function of time were calculated by using Kaplan-Meier analysis up to 3.6 years after first stroke.
Stromberg et al [114]	Cumulative risk of recurrent stroke was estimated at 2, 5 and 30 days after first stroke using Kaplan-Meier curves.
Kumral et al [115]	Kaplan-Meier and log-rank tests used to determine the relationship between LA and recurrent stroke up to 5 years after first stroke. Cox proportional hazards models used to identify predictors.
Schmitz *et al* [116]	Cox regression analysis was used to compute adjusted hazard ratios for all long-term outcomes and long-term estimates of recurrent ischaemic stroke risk.
Aarnio *et al [117]*	Cumulative risk of stroke recurrence estimated up to 17 years after first stroke.
Pennlert *et al [118]*	Cox regression was used to identify predictors of stroke recurrence up to 5 years after first stroke.
Ntaios *et al [119]*	Kaplan-Meier product limit method and Cox proportional hazards models used to estimate cumulative risk and predictors of stroke recurrence up to 10 years after first stroke.
Lau *et al [120]*	Cox regression models were used to identify predictors of recurrent stroke up to 5 years after first stroke.
Kim *et al [121]*	Kaplan-Meier estimates and Cox regression analysis determine the relationship between leukoaraiosis burden and symptomatic stroke recurrence up to 90 days after first stroke.
Poon *et al [122]*	Meta-analysis pooling of cumulative risk of recurrent ICH up to 1 year and 5 years after first CH

Table 10. Identified studies using methods to estimate cumulative risk to assess the risk of stroke recurrence over 2 year period

Study authors/group	Statistical methods used
Mono *et al [123]*	Recurrence-free survival time assessed using life- table analysis Estimates were given at time-points: (i) within 72 hours of admission, (ii) in the period from 72 hours to 7 days, and (iii)after 7 days, in patients presenting with non-disabling stroke, transient ischemic attack (TIA), or amaurosis fugax and with an ipsilateral symptomatic CA stenosis of 50% or more.

Table 11 Study identified using defined time periods to assess the risk of stroke recurrence over 2 year period

Finally, the use of defined time periods assumes the risk of stroke recurrence in that time period is independent to the risk estimated in the preceeding time-period, e.g. that the risk of stroke recurrence from 1 to 5 years is independent of the risk estimated from 0 to 1 year. There are many reasons why this may not be the case, including late identification of risk factors during follow-up, or non-adherence to prescribed medication, Time-dependent covariates may provide a better option allowing post-stroke risk factors to be included in analyses. The use of time-dependent covariates in the estimation of predictors of stroke recurrence shall be discussed further in Chapter 6.

Since the start of the SLSR in 1995, the pathological Oxford Community Stroke Project (OCSP) classification of stroke subtype has been introduced, as well as an aetiological classification system based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[20], modified in South London to improve the rate of determined aetiology and to account for expected differences in stroke subtype for the local black population[82]. As both these classifications have previously been validated to be applied retrospectively as well as for prospective use, this provides an opportunity for patient records to be reviewed, in order to determine the OCSP and modified TOAST stroke subtypes for any outstanding patients[15].

Furthermore, it is important to ensure complete case ascertainment, in particular by identifying patients who may have had a stroke recurrence prior to death. The SLSR uses 16 overlapping notification sources with high levels of capture-recapture consistently observed in analyses[14, 124]. However, whilst death data related to register participants are obtained regularly from the Office for National Statistics (ONS), there has previously been no further review of this data to see if a stroke recurrence occurred prior to death. Due to the high quantity of data received since 1995, it is impossible and impractical to review every single set of hospital and community notes to ascertain if a stroke recurrence, not previously recorded by the SLSR, occurred. The use of an algorithm based on the International Classification of Disease (ICD-9 or ICD-10) codes related to stroke, may help to identify patients, who, by the code given to their cause of death and other pre-morbid conditions, may have had a further stroke before their death.

In this study, a Cox Proportional Hazards model was used to identify predictors of stroke recurrence. Cox Proportional Hazards models make no assumption about the form the underlying hazard of stroke recurrence takes[125]. Previous population-based studies have used Cox models to undertake these analyses[97, 126], however no studies have been found that identify the form of the hazard distribution. By using a non-specific statistical model such as the Cox model, the risk of stroke recurrence, and by default the effect of predictors of the risk of stroke recurrence may be under-estimated or over-estimated.. It would therefore be useful to clarify the distribution of the risk of stroke recurrence by fitting different statistical models to results, using a sufficiently large data sample, in order to ascertain the best fit model. This shall be explored further in Chapters 4 and 5 of this thesis.

3.5 Summary

This preliminary study has shown that cardiovascular risk factors do have an important role in predicting the risk of stroke recurrence. However it also identified several factors to be addressed both methodologically and regarding the dataset used, prior to further analyses being conducted.

Ensuring completeness of both case ascertainment and variables with missing data, where retrospective data collection is possible and has been validated e.g. the TOAST classification, is important for results to be as accurate as possible, and so that the right conclusions are made.

Identification of the distribution of the risk of stroke recurrence is also important in order for the most accurate statistical model to be used in the analyses. In order for the correct model to be fit to the distribution, a large sample of data is needed. This shall be explored further in the next chapter.

Chapter 4 Risk and cumulative risk of stroke recurrence: a systematic review of the literature and meta-analysis

This systematic review and meta-analysis was presented as oral presentations at the UK Stroke Forum in 2009 and the European Stroke Conference in 2010 and was published in 'Stroke' journal in 2011. (See Appendix 1).

Abstract

Background- Estimates of risk of stroke recurrence are widely variable and focused on the short-term. A systematic review and meta-analysis was conducted to estimate the pooled cumulative risk of stroke recurrence at different time-points after first-ever stroke and to determine the influence of the socio-demographic and clinical risk factor profile of the study populations, as well as study design and methodological factors on reported risk of stroke recurrence.

Methods- Studies reporting cumulative risk of recurrence after first-ever stroke were identified using electronic databases and by manually searching relevant journals and conference abstracts. Overall cumulative risks of stroke recurrence at 30 days and 1, 5, and 10 years after first stroke were calculated using inverse-variance methods, and analyses for heterogeneity were conducted. Non-linear least squares analyses were used to fit statistical models to the pooled results to estimate the cumulative risk of stroke recurrence over time.

Results- Sixteen studies were identified, of which 13 studies reported cumulative risk of stroke recurrence in 9115 survivors. The pooled cumulative risk was 3.1% (95% CI, 1.7-4.4) at 30 days, 11.1% (95% CI, 9.0-13.3) at 1 year, 26.4% (95% CI, 20.1-32.8) at 5 years, and 39.2% (95% CI, 27.2-51.2) at 10 years after initial stroke. Substantial heterogeneity was found at all time points with I^2 values ranging from 88-96%. The results also demonstrate a temporal reduction in 5-year risk of stroke recurrence from 32% to 16.2% across the studies.

Conclusions- The cumulative risk of recurrence varies greatly up to 10 years. This may be explained by differences in case mix and changes in secondary prevention over time However, methodological differences are likely to play an important role and consensus on definitions would improve future comparability of estimates and characterisation of groups of stroke survivors at increased risk of recurrence.

4.1 Background

Patients surviving an initial stroke are known to be at a significantly increased risk of further strokes, compared to the rest of the population however quantification of how great the risk of recurrence is at different time-points after first stroke is limited[36]. Identification of patients at high risk of stroke recurrence at specific time points after first stroke is important in order for modifiable risk factors to be targeted and to prevent reduce the risk of these strokes occurring[37]. There is considerable variation in the risk of stroke recurrence in the reported literature, however reasons for these differences are unclear. For example, the 5 year risk of stroke recurrence has been reported to range from 12-42%[127, 128] with other population-based studies reporting cumulative 5 year risk of 19% in Manhattan and 29% in Rochester, both in the USA; 30% in Oxfordshire, United Kingdom; and 32% in Perth, Australia [17, 91, 129] .Furthermore it is unclear if, despite variations in reported results across different study groups, it is possible to fit a statistical model to combined results to predict the cumulative risk of stroke recurrence over time.

The aim of this systematic review is to examine the literature related to risk of stroke recurrence at different time-points after first-ever stroke and to determine the influence of the socio-demographic and clinical risk factor profile of the study populations, as well as study design and methodological factors on reported risk of stroke recurrence.

4.2 Methods

4.2.1 Identification of papers

This review aims to identify all studies from hospital-based or community-based stroke registers reporting the risk of stroke recurrence at any time point after first-ever stroke irrespective of study design and setting, or language. Ovid Medline (1950-December 2009), EMBASE (1950-December 2009) and the Web of Science were searched by use of both the medical subject heading (MESH) terms and free text, combining terms for

stroke (stroke OR cerebrovascular disease OR cerebrovascular accident) AND stroke recurrence (recurren*).

In addition, the reference lists of all identified studies and the contents pages of relevant peer-reviewed journals (Stroke, Lancet Neurology, New England Journal of Medicine, Cerebrovascular Diseases, the Journal of Neurology, Neurosurgery and Psychiatry, and the British Medical Journal), as well as abstracts from national and international conferences related to stroke were hand-searched in order to identify studies not previously identified by the electronic searches.

4.2.2 Inclusion Criteria

This review included studies reporting the risk of stroke recurrence at any time-point after a first-ever stroke. Studies reporting recurrence after ischaemic strokes, primary intra-cerebral haemorrhages, sub-arachnoid haemorrhages and undefined strokes were included. A stroke 'recurrence' was defined as a focal neurological deficit lasting more than 24 hours and occurring after an initial stroke. This definition was utilised in order to include all studies reporting stroke recurrence at any time point after a first stroke. Studies reporting data from both hospital-based and population-based stroke registers were included, however, studies reporting on only a particular subset of patients (e.g. diabetic patients or men only) were excluded. Multiple publications from the same study group, were reviewed to avoid the use of the same data from over-lapping cohorts.

The meta-analyses included studies reporting the cumulative risk of stroke recurrence, estimated using survival analysis (time to stroke recurrence) methods, only. Data were extracted from studies to undertake estimates of pooled cumulative risk of stroke recurrence at 30 days, 1, 5 and 10 years after initial stroke.

4.2.3 Data extraction

A matrix was used to extract information from the included studies. This is summarised in Figure 3.

Study group/country
Study period
Length of follow-up period
Clinical setting
Inclusion criteria for study
Definition of stroke
Definition of stroke recurrence
Exclusion period before stroke recurrence defined
Population characteristics
Socio-demographic factors
Prior-to-stroke risk factors
Stroke severity markers
Subtype of initial and recurrent stroke
Outcome measures
Risk of stroke recurrence at any reported time-points
Cumulative risk of stroke recurrence at any reported time-points

Figure 3. Data extracted from included studies

4.2.4 Data collection

In instances where incomplete data were obtained from included publications, the authors were contacted in writing, for permission to obtain data for further analyses. This was repeated if no response was received within 2 weeks, and further correspondence contacts were sought and contacted if available.

4.2.5 Data analyses

The risk of stroke recurrence, i.e. the probability of a stroke recurrence having occurred by a given time-point, was obtained directly from the studies included in the systematic review. Additionally, the cumulative risk of stroke recurrence, defined as the probability that an individual will have a stroke recurrence at a given time-point assuming that they do not die from some other cause[130], and related 95% Confidence Intervals (CI) were calculated 30 days, 1, 5 and 10 years after first stroke for individual studies and pooled estimates were derived.

Inverse-variance methods were used to calculate the pooled estimates and associated 95% CIs[131]. Due to presumed differences in study design across the 13 studies, the Der Simonian and Laird method of random effects meta-analyses was used[132]. In a random-effects meta-analysis, the standard error of the study estimates are adjusted to account for heterogeneity among the estimates observed in different studies

Forest plots were constructed for each time point (30 days, 1, 5 and 10 years after first stroke). Analyses for heterogeneity were conducted using the Chi-squared test. A sensitivity analysis was conducted to compare the pooled cumulative risk at 1 year after first stroke, for hospital and community-based stroke populations.

Non-linear least squares analyses were used to construct Exponential and Weibull random effects meta-regression models. These models were fit to the risk of stroke recurrence, estimated in the individual studies, to establish the model of best-fit and to model cumulative risk as a function of time since first stroke. The Weibull (a generalisation of the exponential distribution) was the simplest model providing an adequate fit to the meta-analytic estimates of stroke recurrence [125]. The use of these models allowed for the prediction of the cumulative risk at time-points not directly analysed in the meta-analysis. The model assumed that the cumulative risk followed a

Weibull distribution with a bivariate random effects model for the study specific parameters.

Analyses were conducted using SPSS Version 17, Review Manager Version 5 and PROC NL MIXED of SAS version 9.1. SPSS was used to estimate the cumulative risk and corresponding 95% Confidence Intervals for studies where raw data was obtained from the study authors. Review Manager was used to obtain the pooled estimates and construct Forest plots for each time point. Finally SAS was used to fit statistical models to the pooled results to allow estimation of the cumulative risk of stroke recurrence at time-points not directly analysed in the meta-analyses.

4.3 Results

2497 studies were identified by the electronic database searches, of which 24 studies met our inclusion criteria. A further 4 studies were added by hand-searching journals and conference abstracts related to stroke. Therefore, a total of 28 studies reporting the risk of stroke recurrence were included in this review.

4.3.1 Risk of stroke recurrence

The risk of stroke recurrence, i.e. the probability of a stroke recurrence having occurred by a given time-point, was reported to range from 1.1% in South London[133] to 15% in Oxfordshire, UK[134] by 1 month; from 7.0% in Lisbon, Portugal[135] to 20.6% in Nanjing, China[103] by 1 year; from 16.2% in South London[133] to 35.3% in Hisayama, Japan by 5 years[136]; and from 14% in Rome, Italy[137] to 51.3% in Hisayama, Japan[136] by 10 years post-initial stroke. Figure 4 shows the estimates of risk of stroke recurrence up to 10 years after initial stroke, across all the included studies. It is notable that the range of estimates reported between studies increases as time since first stroke increases.

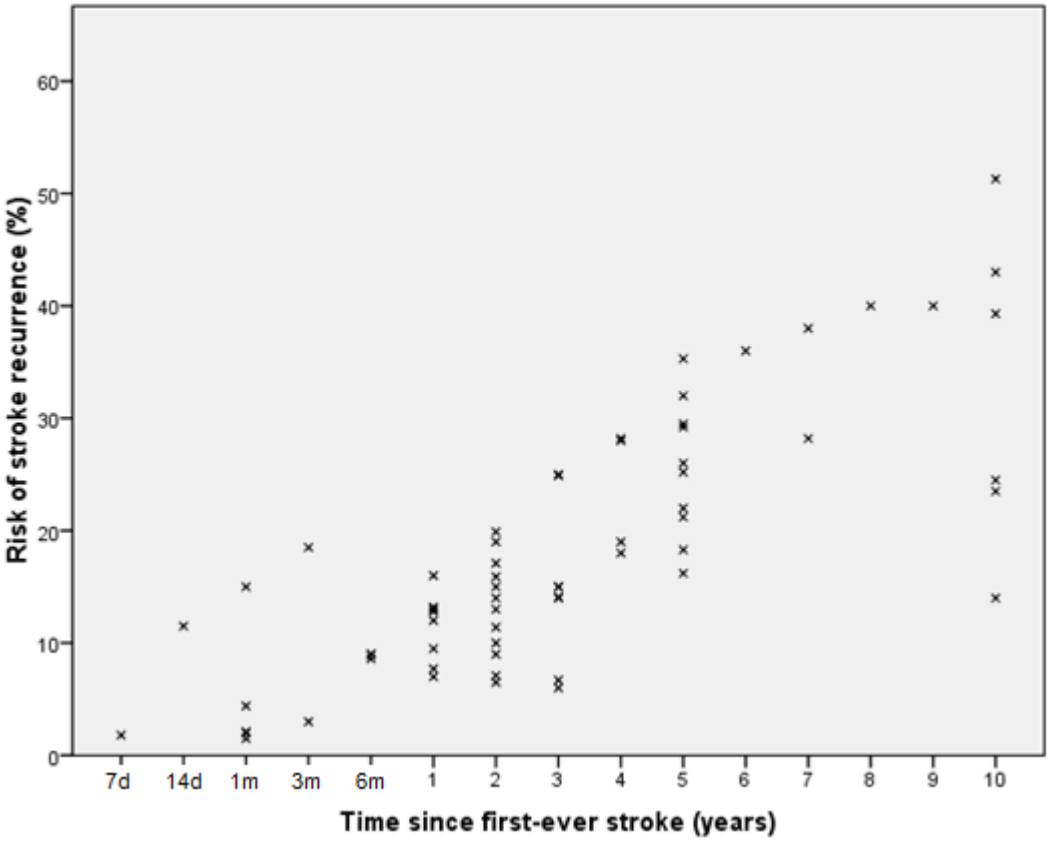

Figure 4. Risk of stroke recurrence after first stroke across all 16 included studies.

4.3.2 Cumulative risk of stroke recurrence

16 studies reporting the cumulative risk of stroke recurrence were identified of which, from 13 studies sufficient data was obtained to be included in the meta-analysis. The cumulative risk of stroke recurrence, was defined as the probability that an individual will have a stroke recurrence at a given time-point assuming that they do not die from some other cause and is estimated using survival or time-to-event analyses [130]. The breakdown of studies included in the analyses is displayed in Figure 5.

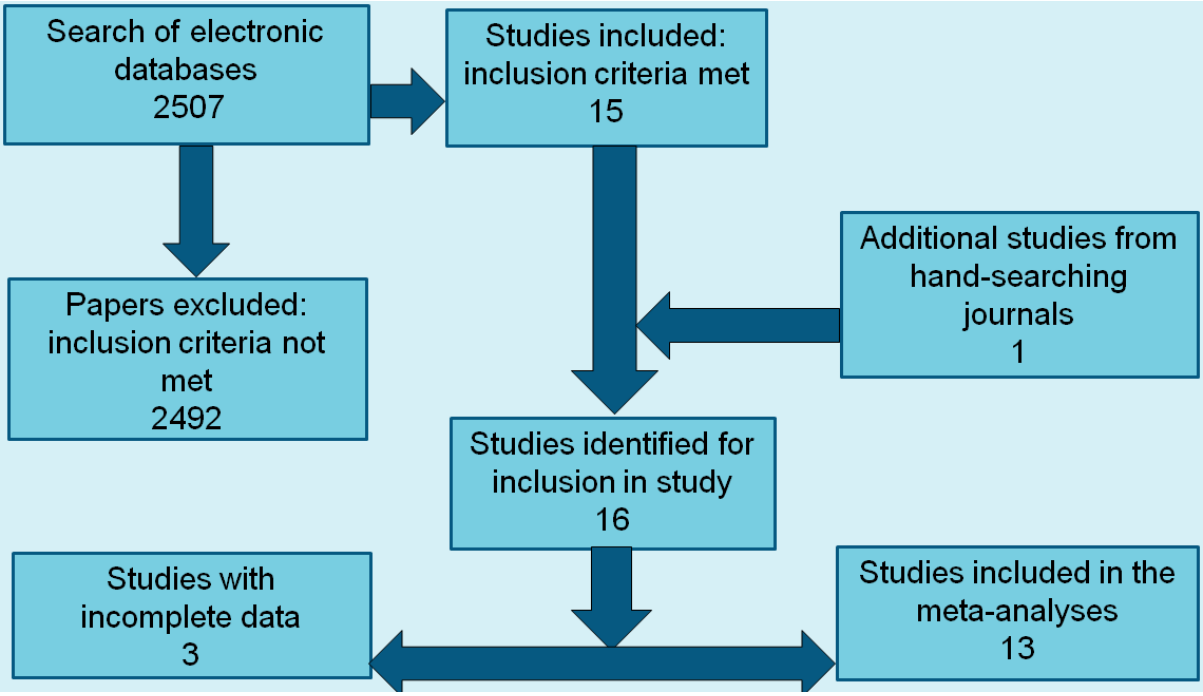

Figure 5. Systematic review flowchart

For the three studies not included in the study, repeated attempts were made to obtain data at the time-points needed to be included in the study, however, this data was not available. A summary table with details of these three studies is shown in Table 12.

Authors	Population studied	Reason for exclusion
Lai *et al[138]*	Lehigh Valley Recurrent Stroke Study	Kaplan-Meier estimates at 3 months presented without standard error. Unable to contact study investigators to obtain more data to conduct analyses despite multiple attempts
Elneihoum *et al[104]*	Malmo Stroke Registry (STROMA)	Kaplan-Meier estimates at 3 years estimated as 6% but presented without standard error. Despite multiple correspondences, the data was unable to be located by the Malmo Stroke Registry team.
Acciarresi *et al[139]*	Perugia Stroke Unit, Italy. Hospital based study.	Kaplan-Meier estimate at 3 months presented without standard error. Unable to contact study investigators to obtain more data to conduct analyses despite multiple attempts

Table 12 Studies unable to be included in meta-analyses due to incomplete data

Key details of the 13 studies included in the meta-analysis are displayed in Table 13 (table over 3 pages). Table 14 displays the estimates of cumulative risk of stroke recurrence up to 30 days, 1 year, 5 years and 10 years after first stroke in the studies included in the meta-analysis.

Authors	Stroke study	Initial study period	Setting	Study design	Stroke defined	F/U period
Hardie	Perth Community Stroke Study	1989-1990	Population-based	Prospective	WHO criteria	10 years
Petty	Rochester Epidemiology Project	1975-1989	Population-based	Retrospective using Medical records linkage system	WHO criteria. CT to exclude ICH/SAH	5 years
Dhamoon	Northern Manhattan Stroke Study	1983-1988	Population-based	Prospective	WHO criteria	5 years
Burn	Oxfordshire Community Stroke Project	1981-1986 (except Nov 1984-5)	Population-based	Prospective. Recruitment from GP practices in defined study area.	WHO criteria	6.5 years
Hata	-	1961-1993.	Hospital based	Prospective	WHO criteria	10 years
Modrego	-	1997-2001	Hospital-based	Prospective	WHO criteria	6 years
Kolominsky-Rabas	Erlangen Stroke Project	1994-1998	Population-based	Prospective	WHO criteria	2 years
Xu	Nanjing Stroke Registry Program	2002-2006	Hospital based	Prospective	WHO criteria	1 year
Salgado	-	1990-1993	Hospital-based	Prospective		4 years
Appelros	-	1999-2000	Population-based	Prospective	WHO criteria	1 year
Coull	Oxford Vascular Study	2002-2003	Population-based	Prospective. Same as Burn *et al* study.	Minor stroke NIHSS ≤ 3 at time of initial event	3 months
Mohan	South London Stroke Register	1995-2004	Population-based	Prospective	WHO criteria	10 years
Rundek	Northern Manhattan Stroke Study	1990-1995	Hospital-based	Prospective	WHO criteria	4 years

Authors	How followed up	Initial stroke exclusion criteria	Exclusion period for recurrence
Hardie	Medical record f/u at 4 months and 1 year; interview at 5 years; postal questionnaire and telephone interview at 10 years	Nil	21 days after initial
Petty	Medical record review	People living in area less than 1 year;	Nil
Dhamoon	6 month telephone evaluation, then annual face-to-face follow-up	Ischaemic stroke only; age over 40; resident in area greater than 3 months; has telephone	Nil
Burn	1 month, 6 months, 1 year and then annually face-to-face follow-up interview	First ever stroke or TIA	21 days after initial unless different vascular territory or if SAH.
Hata	Follow up every 5 years	Age >40 years	Nil
Modrego	-	No SAH	Nil
Kolominsky-Rabas	28 days, 3 months, 1 and 2 years	Nil	24 hours after initial stroke. Within 21 days reviewed to ensure not extension
Xu	Every 2-3 months after initial stroke	Ischaemic stroke only. Need to have seen neurologist within 7 days and had CT/MRI; aged 18 years or over	Nil
Salgado	Every 3 months up to 1 year, then every 6 months to 5 years	Lacunar infarction only.	Nil
Appelros	1 year face-to-face follow up	SAH excluded	4 weeks after initial (MONICA criteria)
Coull	7 days, 1 month, 3 months	Stroke severity >3 on NIHSS.	Nil
Mohan	3months, 1 year, then annually to 10 years. Face to face if possible, or else telephone.	Nil	21 days after initial unless different vascular territory
Rundek	6 month telephone evaluation, then annual face-to-face follow-up	Ischaemic stroke only; age over 40; Northern Manhattan community resident;	Nil

Authors	How recurrence defined
Hardie	As for stroke
Petty	As for stroke. Autopsy evidence of recent infarction in different vascular territory if date of recurrence can be estimated.
Dhamoon	As for stroke. In addition the presence of a new neurological deficit, evidence of different vascular territory, or acute focal neurology after "stabilisation of initial stroke required.
Burn	Stroke only (not TIA). Clinically apparent events only.
Hata	As for initial stroke. In addition, new focal neurological deficit or a new deterioration of a previous deficit that was not attributed to brain oedema, haemorrhagic transformation after ischaemia, intercurrent illness, or iatrogenesis was required
Modrego	As for stroke
Kolominsky-Rabas	As for stroke. In addition the presence of a new neurological deficit, not attributable to oedema, haemorrhagic transformation, mass effect, or brain shift syndrome was required.
Xu	As for stroke. Clinically apparent events only
Salgado	Acute focal neurology after "stabilisation of initial stroke"
Appelros	As for stroke.
Coull	Stroke only (not TIA). Clinically apparent events only.
Mohan	As for stroke. In addition the presence of a new neurological deficit, or deterioration of a previous deficit not due to oedema, haemorrhagic transformation, or intercurrent illness was required.
Rundek	As for stroke. In addition the presence of a new neurological deficit, evidence of different vascular territory, or acute focal neurology after "stabilisation of initial stroke required.

Table 13. Characteristics of studies included in the meta-analyses.

Authors	Population studied	Initial study period	Number in study	Cumulative risk of stroke recurrence (%)			
				30 days	1 year	5 years	10 years
Hardie et al[140]	Perth, Australia	1989-1990	328	2.1	16.0	32.0	43.0
Petty et al[17]	Rochester, USA	1975-1989	1111	4.4	12.0	29.2	39.3
Rundek et al[141]	Northern Manhattan, USA	1990-1995	611	2.9	9.8	-	-
Dhamoon et al[142]	Northern Manhattan, USA	1983-1988	655	1.5	7.7	18.3	-
Burn et al[129]	Oxfordshire, UK	1981-1986	675	-	13.2	29.5	-
Coull et al[134]	Oxfordshire, UK	2002-2003	87	15.0	-	-	-
Kolominsky-Rabas et al[143]	Erlangen, Germany	1994-1998	583	-	11.0	-	-
Mohan et al[133]	South London, UK	1995-2004	2874	1.1	7.1	16.2	24.5
Hata et al[136]	Hisayama, Japan	1961-1993	410	-	12.8	35.3	51.3
Modrego et al[144]	Bajo Aragon, Spain	1997-2001	425	-	9.5	26.0	-
Appelros et al[145]	Orebro, Sweden	1999-2000	377	-	9.0	-	-
Xu et al[103]	Nanjing, China		834	13.3	20.6	-	-
Salgado et al[135]	Lisbon, Portugal	1990-1993	145	-	7.0	-	-

Table 14. Cumulative risk of stroke recurrence, by study.

The pooled cumulative risk of stroke recurrence was 3.1% (95% CI 1.7-4.4) at 30 days (Figure 6); 11.1% (95% CI 9.0-13.3) at 1 year (Figure 7);26.4% (95% CI 20.1-32.8) at 5 years (Figure 8); and 39.2% (95% CI 27.2-51.2) at 10 years after initial stroke (Figure 9). Substantial heterogeneity was found between the studies at all time points with I^2 values ranging from 88-96%. (No differences were observed when the cumulative risk of recurrence between hospital-based and community-based stroke populations were compared 1 year after first-ever stroke. Significant heterogeneity remained between study estimates within the 2 groups, and therefore results were not stratified according to study population).

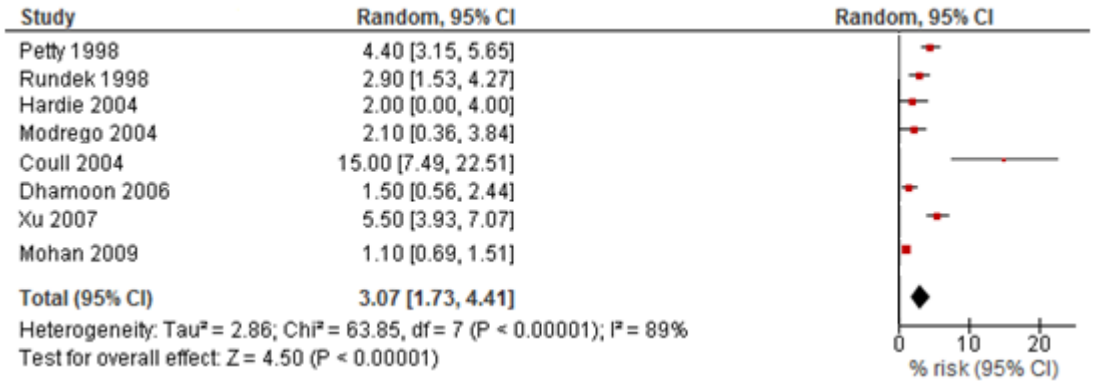

Figure 6. Cumulative risk of stroke recurrence at 30 days post-initial stroke

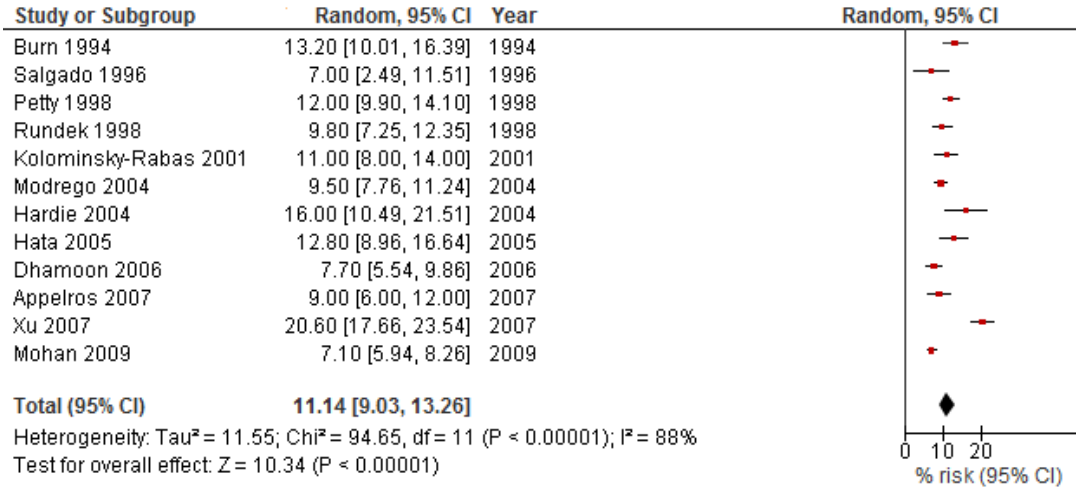

Figure 7. Cumulative risk of stroke recurrence at 1 year post-initial stroke

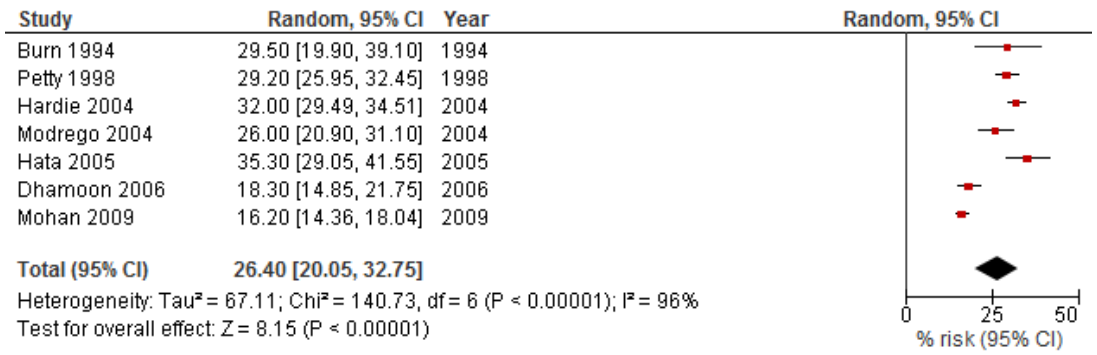

Figure 8. Cumulative risk of stroke recurrence at 5 years post-initial stroke

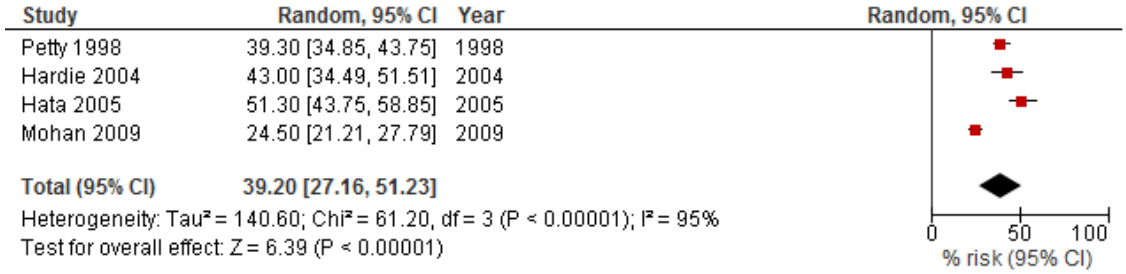

Figure 9. Cumulative risk of stroke recurrence at 10 years post-initial stroke

An Exponential meta-regression model was fitted to the cumulative risk of stroke recurrence of the individual studies and pooled estimates of the cumulative risk of stroke recurrence were calculated with 95% Confidence Intervals (Figure 10)

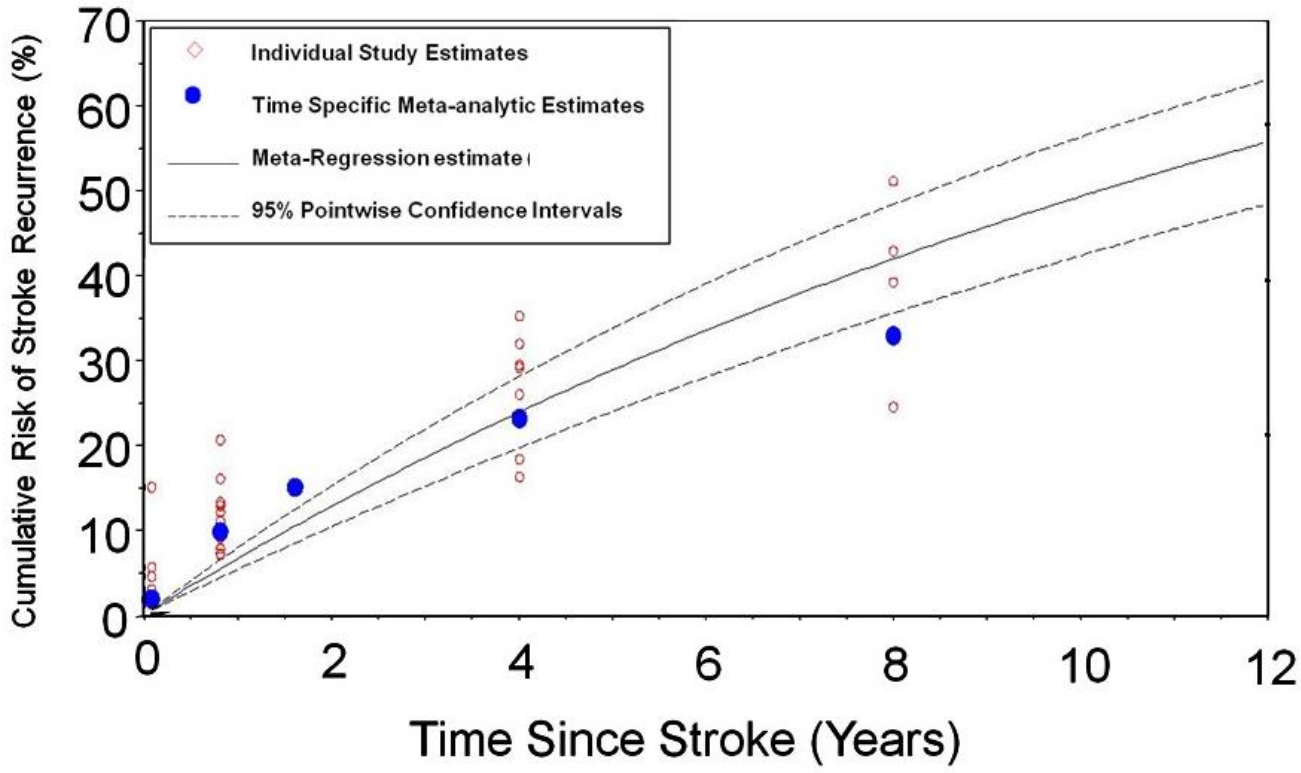

Figure 10. Exponential distribution modelling the cumulative risk of stroke recurrence after first-ever stroke.

As shown in Figure 10, the Exponential model under-estimated the risk of stroke recurrence up to approximately 6 years after first stroke, after which time the model over-estimated the predicted risk.

In order to improve the fit of the pooled estimates to the meta-regression model, a Weibull model was then fit to the cumulative risk of stroke recurrence of the individual studies and pooled estimates of the cumulative risk of stroke recurrence were calculated with 95% Confidence Intervals (Figure 11). It is notable that at each time-point analysed up to 10 year after first-ever stroke, the pooled estimates closely follow the Weibull model.

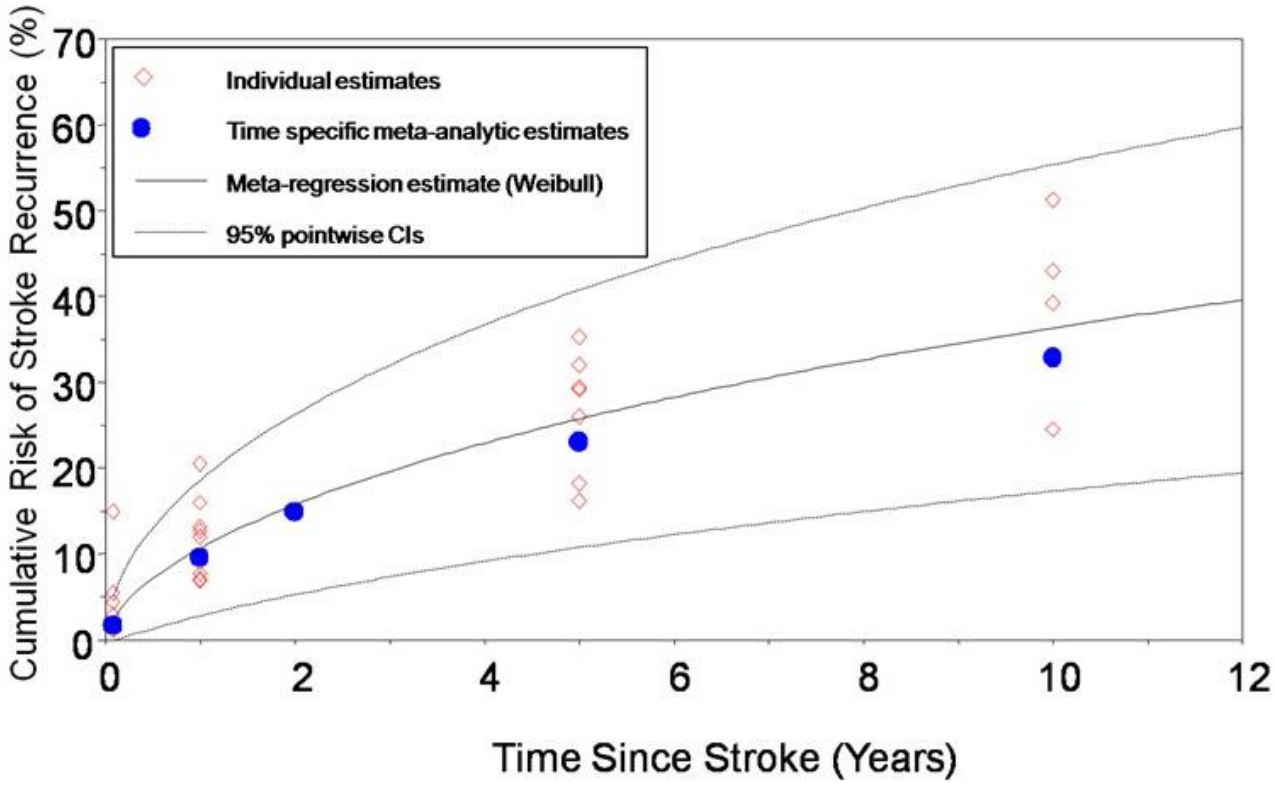

Figure 11. Weibull distribution modelling the cumulative risk of stroke recurrence after first-ever stroke.

4.3.3 Updated literature search results

The literature searches undertaken for this systematic review were completed in November 2009 at which time I was working at the SLSR. For completeness these literature searches were updated in January 2014 to identify any studies published from November 2009 to 11 January 2014 suitable for inclusion in the meta-analyses. A flowchart summary of the studies identified is shown in Figure 12.

A summary table with details of the four studies for full-article review but not meeting the criteria for inclusion in this meta-analysis, is shown in Table 15.

As no studies were identified for inclusion, no further analyses were conducted.

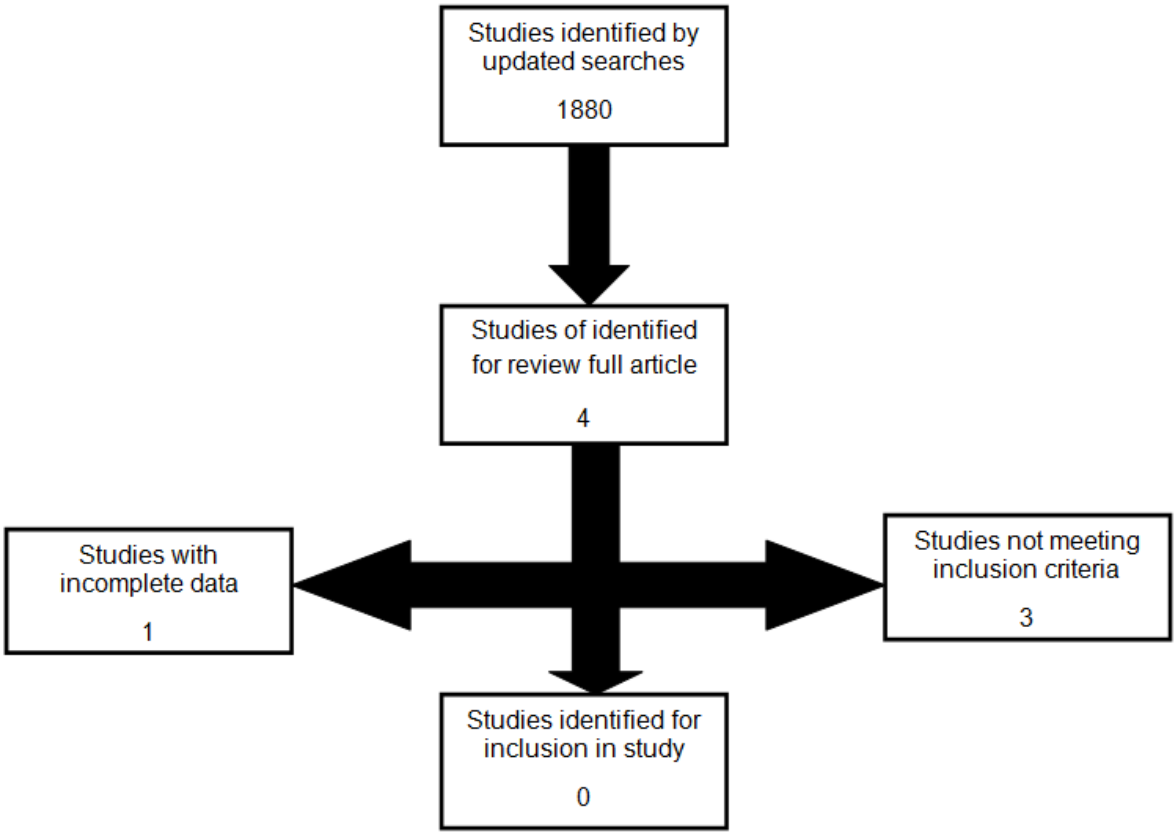

Figure 12 Flowchart of updated literature searches (November 2009- January 2014)

Authors	Population studied	Reason for exclusion
Huhtakangas *et al (2013) [146]*	Northern Ostrobothnia, Finland.	The study investigates the risk of, and predictors for primary intra-cerebral haemorrhage however, includes previous ischaemic stroke as a risk factor.
Feng *et al (2010) [147]*	South Carolina, USA.	This study provides the cumulative risk of stroke recurrence in a cohort of patients admitted with first stroke. The end-point used was a composite measure recording which occurred first of recurrent stroke, MI and vascular death.
Melkas *et al(2012) [148]*	Helsinki, Finland	The study only included patients aged 55-85 years.
An *et al* (2011) [149]	Tangshan, China	It is unclear whether is study reported first-ever strokes only. The full text of the study article was unavailable as it was published in the 'Zhonghua Liu Xing Bing Xue Za Zhi' journal in Chinese only.

Table 15 Studies identified by literature search for full-text review

4.4 Discussion

The results from this systematic review and meta-analysis demonstrate wide variation in the reported cumulative risk of stroke recurrence up to 10 years after first stroke and significant heterogeneity was observed between studies at all time points. This degree of heterogeneity, and its consistency throughout all time-points analysed suggest that the observed differences are unlikely to be due to chance.

Differences in study design and population demographics exist between the included studies, however they share important characteristics as described in Table 13. In particular, the definition of ‘stroke’ and ‘recurrence’ and how participants are followed up are similar across studies, whilst key differences lie in the dates of initial study period, study setting and the use of an exclusion period for recurrent stroke.

Whilst case-mix and differences in prior-to-stroke risk factors between the populations may be responsible in part for these observed variations, differences in case inclusion criteria are also likely to be contributory factors. One possible reason for this is that studies using both hospital and population-based stroke registers were included in the analyses. Not all patients with a stroke present to hospital, either in the acute period or at all, therefore hospital based stroke registers cannot fully ascertain the incidence of initial, or recurrent stroke fully within a population[150] . Furthermore it is impossible to predict which patients are more or less likely to present to hospital after a stroke, as both patients with very mild and very severe strokes may not present to hospital for a variety of reasons[151]. In this meta-analysis, no significant differences were noted between hospital and community-based estimates at 1 year after first-ever stroke, and stratification of results did not remove the observed heterogeneity. This indicates that other factors, are likely to also be important in differences in cumulative risk of stroke recurrence estimated in this study.

Variations in eligibility criteria for study inclusion may also have importance in observed differences between the study groups. Both data from the Northern Manhattan Stroke Study (NOMAS) and the Hisayama study only included stroke patients aged over 40 years of age in their analyses [136, 141, 142] Furthermore NOMAS patients were only included in analyses conducted by Dhamoon et al if they had a telephone in order for a telephone follow-up interview to be conducted six months after their initial stroke[142]. This may result in those from a lower socio-economic background or older patients who may not have access a telephone to be included in the study. Increasing age, and lower socio-economic status have both been previously associated with increased incidence of stroke and stroke recurrence[133, 152], therefore by excluding younger people and those without telephones, these studies may be under–estimating the true incidence of both stroke and stroke recurrence within the source population.

Significantly, studies included in this review differed in the way they defined both a stroke and a recurrence. Modrego *et al* demonstrated recurrence rates of 9.5% at 1 year and 26% at 5 years post-initial stroke, however, this study, is an example of one of many studies which excluded patients with a subarachnoid haemorrhage (SAH) or included ischaemic stroke patients only[144]. Studies from the South London Stroke Register have found that sub-arachnoid haemorrhage confers an increased risk of recurrence in the first six months after initial stroke, after which there is no increase in risk of stroke recurrence reported up to 10 years of follow-up[133]. By excluding this subgroup, artificially higher rates of recurrence may have been achieved in these studies.

The Oxfordshire Community Stroke Project (OCSP) followed up patients for 6.5 years and found a cumulative risk of recurrence of 30% at 5 years[129]. The methodology used by the OCSP investigators included transient ischaemic attacks (TIAs) as an initial stroke event. TIAs can also be considered as a risk factor for strokes, particularly those of an atherosclerotic aetiology[153] and including these events as initial strokes may cause a substantial overestimation in the reported risk of stroke recurrence in this population.

The reported differences in risk of recurrence may also be explained by different definitions of what constitutes a 'stroke recurrence' used between studies. There was wide variation in the definition of stroke recurrence used, ranging from any focal neurological deficit lasting for more than 24 hours occurring after the initial stroke[17, 136, 141, 142] to an exclusion period of 28 days, only after which further strokes would be considered as a 'recurrence'[104, 154]. Investigators of the Vascular Events In Non cardiac Surgery Patients Cohort Evaluation Study (VISION) demonstrated that a high proportion of patients with minor stroke have both clinical and radiological recurrences in the same vascular territory as their initial event in the first days after their stroke, whilst recurrent events outside of the initial vascular territory or perfusion defect were rare[155].

Furthermore, Coull and Rothwell have previously demonstrated the effect of different definitions of stroke recurrence on estimates of risk 90 days reported after initial stroke in the Oxford Vascular Study (OXVASC) and Oxford Community Stroke Project (OCSP) cohorts[156]. They found that the risk of stroke recurrence in OXVASC and OCSP respectively, ranged from 18.3% and 14.5% when including all stroke recurrences occurring 24 hours after the initial stroke, to 5.9% and 4.8% using the definition of only stroke recurrences occurring after 28 days employed in the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study and other population-based studies[141, 156].

This is particularly important when considering the reported risk of stroke recurrence at 30 days, where an exclusion period of 21 or 28 days imposed in some included studies[133, 140], may substantially impact the observed risk of stroke recurrence reported 30 days after initial stroke. In this review, studies excluding recurrences occurring in the first 21 days after initial stroke were at the lower end of estimates of risk of stroke recurrence reported at 30 days[133, 140]. However, the effect of excluding recurrent strokes in the first weeks after initial stroke may be seen in reported risks of stroke recurrence into the long-term period. It is known that, in particular, strokes with

an atherosclerotic origin recur earlier than other stroke subtypes, and therefore by excluding recurrent strokes occurring in these critical first weeks after initial stroke, artificially lower risk of stroke recurrence may be reported[104].

The studies included in this review have a combined study period encompassing fifty years (Table 14). Temporal trends in stroke management and, in particular, the advent and increasing importance given to secondary prevention after initial stroke, may be another important contributory factor of variation in the risk of stroke recurrence during this period. In particular, Figure 8 largely demonstrates a temporal reduction in the risk of stroke recurrence, across the different study populations, with smaller recurrence risk reported in later studies. The exception to this is the study performed by Hata *et al*[136]. This population reported very high rates of recurrence after haemorrhagic strokes, and in particular subarachnoid haemorrhage, with high rates of stroke recurrence maintained up to 10 years after initial stroke, making this study distinct when compared to the other included studies. Differences in the source population may play an important role in explaining these findings, however further investigation is needed in this area.

These analyses provide long-term pooled estimates of cumulative stroke recurrence risk up to 10 years after first stroke. High levels of heterogeneity indicated by I^2 values ranging from 88-96% were observed at across all time-points. Random-effects models were used in the meta-analysis to account for heterogeneity between studies as differences in study design were presumed across the 13 studies. However, the effect of variation in population demographics, and indeed temporal trends described briefly in this section, may be considered as reasons for pooling of estimates across study populations not to be undertaken.

Advances in both secondary prevention and radiological imaging have changed the way stroke and recurrence are both identified and managed over the last decades. However evidence for variation in stroke recurrence rates worldwide due to population

demographics or temporal trends due to temporal trends, which may preclude from estimates being pooled, are lacking.

In particular, meta-analyses investigating the differences in stroke incidence and stroke subtypes in Chinese compared to white populations have described a higher proportion of intracerebral hemorrhage in Chinese populations, but found no evidence for different distributions of ischemic stroke subtypes and associated risk factors[157, 158]. The study by Xu *et al* from the Nanjing Stroke Registry included in the meta-analysis, estimates the cumulative risk of recurrence in patients with first ischaemic stroke only[103].

Comparison of stroke recurrence risk across study populations is widely described in the literature and the purpose of this chapter has been to highlight differences between study populations and potential reasons for differences in estimates. Clearly, the use of comparable, population-based case ascertainment and similar classification methods across different study populations would allow more in-depth comparisons regarding the cumulative risk of stroke recurrence to be drawn between study populations.

4.5 Summary

In conclusion, this review and meta-analysis has found substantial variation and heterogeneity in the reported risk of stroke recurrence at time points ranging from 30 days to 10 years after initial stroke and a temporal reduction in the risk of stroke recurrence across the different study populations, with smaller recurrence risk reported in later studies. Whilst many methodological factors may play a part, this review has demonstrated that genuine differences between populations and temporal changes in stroke management and secondary prevention may also be important in explaining these results. This indicates that further research is therefore needed to investigate the effect of secondary prevention measures on the risk of stroke recurrence at different time-points ranging from the first weeks to beyond 10 years after first stroke. These questions shall be addressed later in this thesis.

Chapter 5 The cumulative risk of stroke recurrence

The analyses described in this chapter were displayed as a poster presentation at the European Stroke Conference in 2011 (Appendix 1).

Abstract

Background - Data reporting long-term patterns of cumulative risk of stroke recurrence between different aetiological and pathological stroke subtypes are lacking. Furthermore, information regarding transition in subtype of first and recurrent stroke is not widely available.

Methods - Patients registered with the SLSR were followed up for a maximum of 12 years. Kaplan-Meier estimates were used to assess cumulative risk of stroke recurrence and this was stratified to investigate time trends and by using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) and Oxford Community Project Classification (OCSP) classifications. Initial and recurrent stroke subtypes were cross-tabulated to calculate transition probabilities.

Results- Between 1995 and 2009, 4023 patients with first-ever stroke were included in the SLSR. Mean follow-up period was 3.0 years. In 11981.7 person-years of follow up, 394 recurrent strokes were documented. The overall cumulative risk of stroke recurrence was to estimated to be 6.7% by 1 year, 15.1% by 5 years, 21.5% by 10 years and 23.5% by 12 years after first stroke. Time trends indicated a significant reduction in risk of stroke recurrence up to 1 year after first stroke between 1995-1999, 2000-2004, and 2005-2009 (p=0.03).

Between 1999 and 2009, the cumulative risk of stroke recurrence 1 year post stroke ranged from 4.0% in the small vessel occlusion (SVO) group to 6.5% in the large artery occlusion (LAA) group. These results were lower than 1 year recurrence rates for both

intracerebral (PICH) and sub-arachnoid (SAH) haemorrhages which were 8.6% and 8.8%. Transition in aetiological subtype between initial and recurrent stroke was seen in 51.0% at 1 year, increasing to 61.9% 10 years after first stroke.

Conclusions- The cumulative risk of stroke recurrence is wide-ranging between aetiological and pathological subtypes. Further research is needed to identify predictors for increased risk of recurrence amongst different stroke subtypes and to investigate whether implementation of intensified secondary prevention medication can reduce the long-term risk of stroke recurrence.

5.1 Background

Accurate identification of the time after first stroke when a recurrence is most likely to occur is important for both targeted secondary prevention therapy regimes to be developed, as well as to predict outcome after stroke[159]. This time of increased risk may be different depending on the subtype of initial stroke. However most studies have stratified strokes using pathological classifications only, i.e. differentiating between ischaemic and haemorrhagic strokes, and focussing on the first years after first stroke.

As reported in Chapter 3, previous studies from the SLSR have found no differences in the risk of recurrence between ischaemic and haemorrhagic strokes up to 10 years after first stroke[133]. However, this contrasts with both research from Japan that found the risk of stroke recurrence to be significantly greater within 1 year of the first-ever stroke in patients with an initial ischaemic stroke compared with haemorrhagic stroke, and results from the Perth Community Stroke Study (PCSS) who reported prognostic factors for recurrent stroke up to 5 years after first stroke to be an initial stroke subtype of either PICH or SAH[91, 136].

There have been limited population-based studies investigating differences in recurrence rates between the aetiological ischaemic stroke subtypes, and in particular, looking beyond the first few years after initial stroke. It is also unclear whether stroke

recurrences are likely to be of the same aetiological subtype as the first stroke. This is important as it is known that some aetiological subtypes are more closely linked to specific risk factors. Therefore knowledge of which subtypes are more likely to recur, should both help critical time-periods to be identified, as well as allowing modifiable risk factors to be targeted in order to prevent stroke recurrence[20].

The aim of this study was to estimate the risk of stroke recurrence up to 12 years after first-ever stroke, and to estimate the percentage transition of aetiological subtype between first and recurrent (second) strokes recorded at the South London Stroke Register.

5.2 Methods

The use of the South London Stroke Register as the study population, the case ascertainment and data collection methods used in this chapter have previously been described in Chapter 2 of this thesis.

5.2.1 Variable definition

Stroke was defined according to the World Health Organisation (WHO) criteria[81]. Pathological stroke subtypes were classified using neuroradiology or necropsy results into ischaemic stroke, primary intracerebral haemorrhage or subarachnoid haemorrhage.

Ischaemic strokes occurring from January 1999 were further investigated according to an investigation algorithm and categorised by a study clinician into aetiological subtypes according to the TOAST classification[20] with local modifications to improve investigation rates in different ethnic groups[82]. Ischaemic stroke subtypes included in this thesis were defined as: large artery atherosclerosis (LAA) (including extracranial

large artery atherosclerosis and intracranial large artery atherosclerosis), cardio-embolism (CE), small vessel occlusion (SVO), other aetiology (OTH) (including other vascular aetiology, other haemoglobinopathy aetiology, other hypercoaguable aetiology, migrainous stroke, and other aetiology not previously mentioned) and no aetiology identified (UND).

The definition of stroke recurrence was the same as for the index stroke. Additionally, clinical diagnosis of a new neurological deficit, or deterioration of a previous deficit not due to oedema, haemorrhagic transformation, or inter-current illness was required. Only recurrences 21 days after the initial event, or if earlier, clearly in a different vascular territory were included. The same referral sources were used for notification of stroke recurrences as for initial stroke ascertainment. All patients were eligible for follow-up if alive and having reached the specified point of follow-up by August 2010.

5.2.2 Statistical analyses

Univariate analyses using Kaplan-Meier estimates were used to model the risk of recurrent stroke (1- survival free of recurrent stroke) and therefore to measure the cumulative risk of stroke recurrence and 95% confidence intervals (CI) 1, 5, 10 and 12 years after initial stroke. The risk of recurrent stroke was also estimated 1, 5 and 10 years after initial stroke stratified for year of first stroke (categorised as 1995-1999, 2000-2004, 2005-2009).Log rank tests were conducted to estimate differences between the time-periods analysed.

The cumulative risk of stroke recurrence, was defined as outlined in Chapter 2, i.e. the probability that an individual will have a stroke recurrence at a given time-point assuming they do not die from some other cause[130]. Patients were censored at time of death, if lost to follow-up, or if alive at 10 years after stroke. In patients with an initial stroke between 1999 and 2009, the estimated cumulative risk of recurrence was stratified using a modified version of the Trial of Org 10172 in Acute Stroke Treatment

(TOAST) classification[82]. Initial and recurrent stroke subtypes were cross-tabulated to calculate the percentage transition between subtypes up to 10 years after first stroke.

As with the pooled estimates used in Chapter 5, non-linear least squares analyses were used to construct Exponential and Weibull models which were fit to the estimates of cumulative risk of stroke recurrence to establish the model of best-fit and to model cumulative risk as a function of time since first stroke. The Weibull is a generalisation of the exponential distribution, however whilst the exponential assumes that the hazard is constant, the Weibull model allows it to vary. The Weibull was the simplest model providing an adequate fit to the study results therefore more complex modelling was not undertaken[125].

Analyses were conducted using SPSS Version 17 to undertake the cross-tabulation calculations; and SAS version 9.1 to calculate the Kaplan-Meier estimates and to fit the Exponential and Weibull models to the estimates using non-linear least squares analyses.

5.3 Results

5.3.1 Demographic data

This study included a total of 4023 first-ever stroke patients registered between January 1995 and December 2009. The mean follow-up time was 3.0 years, and a total of 11981.7 person years of follow-up were included. During this period, 394 recurrent strokes were documented. Patient characteristics at time of initial stroke are presented in Table 16. The number of patients remaining in the study at key time points during the 12 year study period are summarised in Table 17

	Total, N(%)
Total	4023
Age group	
<65	1248 (31)
65-74	1041 (26)
75-84	1734 (43)
Gender	
Male	2024 (50)
Ethnicity	
White	2890 (72)
Black	805 (20)
Other	225 (5.6)
Socio economic status	
Non-manual	1082 (26)
Manual	2148 (53)
Economically inactive	562 (14)
Unknown	221 (5.5)
Risk factors	
Previous TIA	472 (12)
Hypertension	2436 (61)
Diabetes Mellitus	712 (18)
Previous MI	415 (10)
Previous AF	629 (16)
Smoker or ex-smoker	2404 (60)

Table 16. Baseline demographic data

Time after first stroke	Number at start of time period	Number with stroke recurrence	Number censored - died	Number censored – at last follow-up	Number in study at end of time-period
0-1 years	4023	191 (4.7%)	688 (16.9%)	891 (22.2%)	2253 (56.0%)
1- 5 years	2253	149 (6.6%)	290 (12.9%)	824 (36.6%)	990 (43.9%)
5-12 years	990	53 (5.4%)	165 (16.7%)	660 (66.7%)	112 (11.3%)

Table 17. The number of participants in the study throughout the study-period

5.3.2 Survival Analyses

The cumulative risk of first stroke recurrence was estimated to be 6.7% (95% CI 5.8 to 7.6%) up to 1 year, 15.1% up to 5 years (95% CI 13.5 to 16.7%), 21.5% up to 10 years (95% CI 19.2 to 23.9%) and 23.5% (95% CI 20.6 to 26.4%) up to 12 years after first-ever stroke.

5.3.2.1 Trends in risk of stroke recurrence

The risk of stroke recurrence stratified for year of initial stroke is shown in Table 18. A log rank tested showed significant differences between the risk of stroke recurrence during the three time intervals, up to 1 year ($p=0.03$), 5 years ($p<0.01$) and 10 years ($p<0.01$) after first stroke.

	1 year	5 years	10 years
1995-1999	8.2 (6.6-9.8)	18.6 (16.1-21.1)	26.4 (23.1-30.0)
2000-2004	6.4 (4.8-8.0)	12.5 (10.1-14.9)	18.7 (10.1-27.3)
2005-2009	5.0 (3.5-6.5)	15.8 (8.5-23.1)	-

Table 18 Trends in risk of stroke recurrence up to 10 years after initial stroke from 1995-1999, 2000-2004 and 2005-2009

5.3.2.2 Fitting a model of risk of recurrence

Exponential (Figure 13) and Weibull models (Figure 14) were fit to the estimates to ascertain the best-fit model to predict cumulative risk up to 12 years after first stroke. As can be seen in Figure 13, the exponential model does not closely follow the Kaplan-Meier curve. It under-estimates the risk of stroke recurrence up to approximately five years after initial stroke, after which time it over-estimates the risk. In comparison, the Weibull model is a far better fit to the Kaplan-Meier estimates.

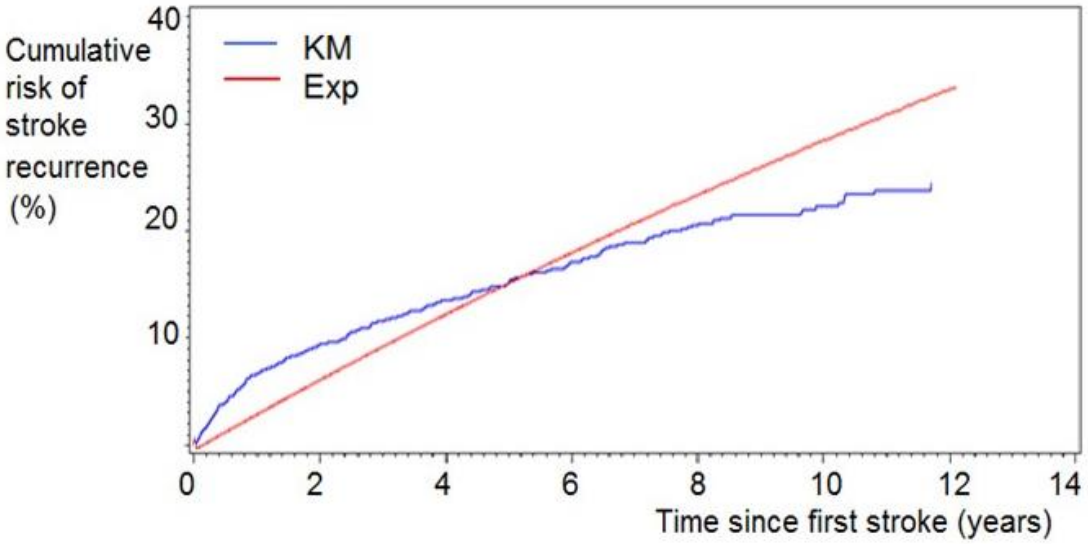

Figure 13 Exponential distribution modelling the cumulative risk of stroke recurrence

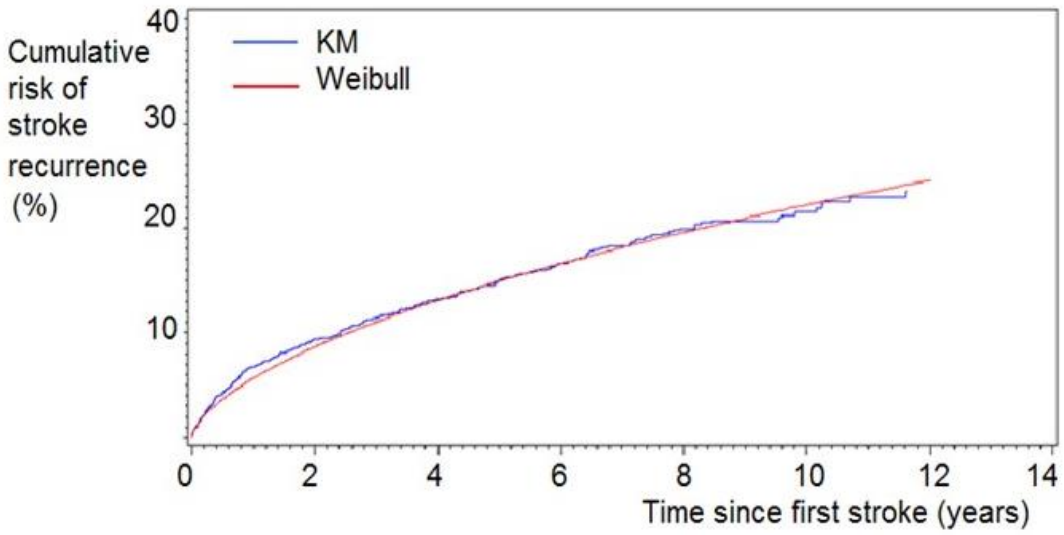

Figure 14 Weibull distribution modelling cumulative risk of stroke recurrence

5.3.2.3 Cumulative risk of stroke recurrence stratified by aetiological subtype

Between 1999 and 2009, 201 stroke recurrences were recorded. The cumulative risk of stroke recurrence, for initial ischaemic strokes occurring between 1999 and 2009 were

stratified according to the modified TOAST classification. These univariate analyses are displayed, compared to the risk of stroke recurrence after an initial PICH or SAH, in Table 19.

Stroke subtype	Cumulative risk of recurrence, % (95% CI)		
	Up to 1 year	Up to 5 years	Up to 10 years
All Ischaemic			
LAA	6.5(2.8-10.2)	14.4(7.3-21.5)	14.4(7.3-21.5)
CE	6.3(3.6-9.0)	15.3(10.4-20.2)	27.1(7.3-46.9)
SVO	4.0(1.3-6.7)	13.5(9.6-17.4)	17.9(12.2-23.6)
OTH	5.4(0.0 -11.3)	10.1(1.5-18.7)	20.1(0.2-40.1)
UND	6.2(4.2-8.2)	12.4(9.6-15.2)	17.0(11.5-22.5)
PICH	8.6(4.5-12.7)	15.0(9.1-20.9)	21.5(8.0-35.0)
SAH	8.8(3.0-14.7)	8.8(3.0-14.7)	8.8(3.0-14.7)

Table 19 Cumulative risk of stroke recurrence stratified by aetiological stroke subtype

Abbreviations: CI: Confidence Interval; LAA: Large Artery Atherosclerosis; CE: Cardio-embolic; SVO: Small Vessel Occlusion; OTH: other; UND: undefined; PICH: Primary Intra-cerebral Haemorrhage; SAH: Subarachnoid Haemorrhage.

5.3.3 Transition between stroke subtypes

Transition in aetiological subtype after 1 and 10 years initial stroke are seen in Table 20 and Table 21 respectively. Table 22 shows transition in stroke subtype between all ischaemic strokes, compared to haemorrhagic strokes. A change in aetiological subtype after initial ischaemic stroke was seen in 47.1% at 1 year, increasing to 53.8% at 5 years and 54.4% 10 years after first-ever stroke. This compared to a 58.3% transition in subtype estimated 10 years after an initial PICH. The transition probability estimated after an initial SAH remained constant at 75% from 1 to 10 years after first stroke, as all recurrences occurred within 1 year of the initial stroke.

		Recurrent stroke subtype n,(%)						
		LAA	CE	SVO	OTH	UND	PICH	SAH
Initial	LAA	8 (72.7)	0 (0)	0 (0)	0 (0)	3 (27.3)	0 (0)	0 (0)
Stroke	CE	0 (0)	15 (71.4)	0 (0)	0 (0)	5 (23.8)	1 (4.8)	0 (0)
subtype	SVO	1 (5.9)	3 (17.6)	5 (29.4)	0 (0)	7 (41.2)	1 (5.9)	0 (0)
	OTH	0 (0)	0 (0)	0 (0)	1(33.3)	1 (33.3)	0 (0)	1(33.3)
	UND	2 (5.7)	2 (5.7)	9 (25.7)	1 (2.9)	17(48.6)	3 (8.6)	1 (2.9)
	PICH	1 (6.7)	4 (26.7)	3 (20.0)	0 (0)	1 (6.7)	6 (40.0)	0 (0)
	SAH	0 (0)	0 (0)	0 (0)	5(62.5)	1 (12.5)	0 (0)	2 (25.0)

Table 20. The 1 year transition in aetiological subtype between first and recurrent stroke

Abbreviations:LAA: Large Artery Atherosclerosis; CE: Cardio-embolic; SVO: Small Vessel Occlusion; OTH: other; UND: undefined; PICH: Primary Intra-cerebral Haemorrhage; SAH: Subarachnoid Haemorrhage.

		Recurrent stroke subtype n,(%)						
		LAA	CE	SVO	OTH	UND	PICH	SAH
Initial	LAA	10 (55.6)	3 (16.7)	0 (0)	0 (0)	5 (27.8)	0 (0)	0 (0)
Stroke	CE	1 (2.6)	24 (61.5)	1 (2.6)	0 (0)	8 (20.5)	4 (10.3)	1 (2.6)
subtype	SVO	4 (8.3)	4 (8.3)	16(33.3)	0 (0)	22(45.8)	2 (4.2)	0 (0)
	OTH	1 (16.7)	0 (0)	1 (16.7)	1(16.7)	2(33.3)	0 (0)	1(16.7)
	UND	2 (3.4)	5 (8.6)	15(25.9)	2 (3.4)	26(44.8)	7 (12.1)	1 (1.7)
	PICH	1 (4.2)	4 (16.7)	3 (12.5)	0 (0)	6 (25.0)	10(41.7)	0 (0)
	SAH	0 (0)	0 (0)	0 (0)	5(62.5)	1 (12.5)	0 (0)	2 (25.0)

Table 21 The 10 year transition in aetiological subtype between first and recurrent stroke.

Abbreviations: LAA: Large Artery Atherosclerosis; CE: Cardio-embolic; SVO: Small Vessel Occlusion; OTH: other; UND: undefined; PICH: Primary Intra-cerebral Haemorrhage; SAH: Subarachnoid Haemorrhage.

	Recurrent stroke subtype		
	All ischaemic	PICH	SAH
Initial stroke subtype n,(%)			
All ischaemic	153 (90.5)	13 (7.7)	3 (1.8)
PICH	14 (58.3)	10 (41.7)	0 (0)
SAH	6 (75.0)	0 (0)	2 (25.0)

Table 22. The 10 year transition in pathological subtype between first and recurrent stroke.

5.4 Discussion

This study provides long-term estimates of the cumulative risk of stroke recurrence up to 12 years after initial stroke. The results indicate that the cumulative risk of first stroke recurrence is substantial (i.e.) up to 23.5% at 12 years post-initial stroke and wide-ranging between aetiological and pathological subtypes over time, with lower 1 year recurrence rates reported in the ischaemic stroke subtypes, compared to the haemorrhagic stroke subtypes. By 10 years, the risk of stroke recurrence amongst the ischaemic subtypes ranged from 14.4% (95%CI 7.3 to 21.5%) to 27.1% (95%CI 7.3 to 46.9), comparable with the 10 year risk of recurrence after PICH of 21.5% (95%CI 8.0 to 35.0) but contrasting with the SAH group, in which the cumulative risk of recurrence remained constant at 8.8% (95% CI 3.0 to 14.7%) from 1 year to 10 years.

The results also demonstrate a temporal decrease in the risk of stroke recurrence after first stroke between 1995 and 2009. In particular the 1 year recurrence rate was estimated to be 8.2% (95%CI 6.6-9.8%) between 1995 and 1999; 6.4% (95% CI 4.8-8.0%) between 2000 and 2004; and 5.0% (95%CI 3.5-6.5%) between 2005 and 2009 (p=0.003). Whilst a reduction in stroke incidence during this time-period has been documented in previous literature, this is the first study to compare temporal trends in risk of stroke recurrence in a population-based setting[14, 15, 160]. The observed risk of stroke recurrence may be due to the increasing use of primary and secondary prevention throughout this time-period. However further studies investigating the effects of secondary prevention on risk of stroke recurrence are needed to test this hypothesis further. This shall be explored more in the next chapter of this thesis.

This study has shown differences in the pattern of stroke recurrence between the different aetiological stroke subtypes. The LAA subtype had the highest risk of stroke recurrence (6.5% (95 CI 2.8-10.2%)) amongst the ischaemic stroke subtypes up to 1 year after first stroke. This was maintained up to 5 years after first stroke, after which time the risk of stroke recurrence in this subtype plateaued. Previous population-based studies have found the risk of recurrence amongst the LAA group to vary widely from 1% at 2 years after initial stroke in Erlangen, Germany[143], to 18.5% at 1 month in Rochester, USA[17]. Furthermore, a meta-analysis performed by Lovett *et al*, studying the risk of recurrent stroke by aetiological TOAST subtype, found patients with the LAA subtype were consistently at 3 times higher risk of stroke recurrence up to 3 months after first stroke, compared to other aetiological subtypes[161]. One reason for observed variation between studies may be that the in order for the LAA subtype to be classified, investigation of the carotid intra and extra-cerebral arteries is essential, without which a diagnosis is unlikely to be made. Adams *et al*, when defining the original TOAST classification, suggested that a large proportion of the UND subgroup had strokes secondary to atheroma[20], indicating that an under-estimation of this sub-group may be occurring within some study groups.

The CE subgroup maintained consistently high levels of stroke recurrence up to 10 years after first stroke. This was also found by Yamamoto et al who used the TOAST classification to examine the aetiological stroke subtype of consecutive stroke recurrences in a hospital-based setting and compared them to the initial stroke subtype. They found a 77% concordance between first and recurrent strokes for the CE subtype, the highest of all the groups studied[162].

Patients with an initial SVO stroke had the lowest risk of stroke recurrence at 1 year, increasing substantially at 5 and 10 years after first stroke. Studies have found the SVO subtype to have both increased odds of an excellent outcome, defined as a combination of a Glasgow Outcome Scale score of 1 and a Barthels Index score of 19 or 20 (on a scale of 0 to 20), at 3 months[163]; to have the highest rates of independent patients, as

defined by Rankin scale scores of 1-2, at 6 months[164]; and to have an increased likelihood of survival at 1 and 2 years after first stroke compared to other TOAST subtypes[165]. Studies from the SLSR have indicated that hypertension may be an important predictor of stroke recurrence up to 5 and 10 years after first stroke. Hypertension is associated with small vessel disease which has been shown to be the aetiological cause related to lacunar infarcts[124] Therefore, patients with small vessel disease have a lower risk of stroke recurrence at 1 year, and may experience stroke recurrence later than other stroke subtypes[133].

The observed difference in risk of recurrence between stroke subtypes highlights the importance of thorough investigation to identify the aetiology of the initial stroke. It is evident that for some stroke subtypes, LAA for example, the critical time period for risk factor management is in the very early period after first stroke, however for the CE subtype this increased risk is sustained into the long-term period and secondary prevention measures should be continued.

The results presented in this chapter are the first results from a population-based stroke register comparing the cumulative risk of recurrence between aetiological stroke subtypes up to 10 years after first-ever stroke. Previous population-based and hospital-based studies have used pathological classifications to compare the risk of stroke recurrence. Results have shown that at 10 years after first ischaemic stroke, 85 to 91% of recurrences were also of an ischaemic pathology[136, 140, 143]. More recently, Hillen *et al* using data from the SLSR, demonstrated change in Oxford Community Stroke Project (OSCP) subtype in 45.5% of patients with a recurrence after first-ever stroke[90].

Hillen also noted that both PICH and lacunar strokes were more likely to change subtype between first stroke and recurrence, compared to initial SAH and non-lacunar strokes[90]. In the analyses from this chapter, strokes of the LAA and CE subtypes were found to have higher levels of same subtype recurrence at all time points up to 10 years

after first-ever stroke compared to the SVO groups. These descriptive analyses are consistent with findings from hospital-based studies, using the TOAST classification to stratify first and recurrent stroke, which have found the PICH and lacunar subtypes to be the most divergent stroke subtypes[136, 162]. Both the PICH and SVO changes are known to occur due to the effect of hypertensive disease on small blood vessels. Lower levels of concordance between first and recurrent stroke in these subtypes may be as a result of the tight control of blood pressure after first stroke. However before associations can be made, further research is needed, to investigate the effect of treated risk factors, such as hypertension, on the short and long-term risk of stroke recurrence.

This study had strengths and limitations. The main strengths lie in study design as by using a population based stroke register as a sampling frame, we have an unbiased sampling frame. Long-term estimates for stroke recurrence up to 12 years after initial stroke have been provided, using standardised methods for comparability to other studies. These analyses also provide aetiological data on ischaemic stroke subtypes, and percentage transition between the different stroke subtypes up to 10 years after first stroke. However, despite the follow-up period being extensive, the number of stroke recurrences obtained and used in particular for the TOAST subtype cross-tabulations are small. Therefore it is was not possible to conduct further analyses identifying predictors for the different aetiological subtypes due to the small numbers of each subtype over the 10 year period.

5.5 Summary

In conclusion, this chapter provides long-term estimates of the cumulative risk of stroke recurrence, and compares the risk of recurrence up to 12 years after first stroke. It has identified aetiological subtypes at increased risk of stroke recurrence at different time-points, and mapped the transition between aetiological stroke subtypes up to 10 years after first-ever stroke. Further research is needed to identify predictors for increased risk of recurrence amongst the different aetiological stroke subtypes and to investigate

whether implementation of intensified secondary prevention medication in high-risk patients can reduce the long-term risk of stroke recurrence.

Chapter 6 The effect of secondary prevention on risk of stroke recurrence

Abstract

Background - Inequalities between patient groups in the use of appropriate secondary prevention medications are known to exist. However, despite these differences, the relationship between the use of these medications and risk of stroke recurrence remains unclear. This chapter examines the association between the use of commonly used secondary prevention medications (anti-hypertensive medication, anticoagulants, lipid-lowering and antiplatelet agents) on risk of stroke recurrence, up to 12 years after first stroke.

Methods – Using data from the SLSR, time-dependent variables were constructed to represent change in use of anti-hypertensive, anticoagulant, lipid-lowering and antiplatelet agents. Time-dependent Cox proportional hazard models were used to estimate the effect of risk factor modification on the risk of stroke recurrence up to 12 years after first stroke in the SLSR population. Subset analyses were conducted to estimate the effect on patients with a first ischaemic stroke only.

Results – A total of 4023 patients with first strokes were followed up for a total of 12 years. Up to 5 years after initial stroke, 322 recurrent strokes were recorded. A non significant decrease in hazard ratios estimating risk of stroke recurrence were observed when patients were prescribed anti-hypertensive, lipid-lowering and anticoagulant medications at any time point during follow-up, compared to patients diagnosed with the relevant conditions but not prescribed medication. The hazard ratios for hypercholesteriolaemia were shown to decrease from 1.46 (95%CI 0.82-2.60) for those not on treatment, to 0.57 (0.34-0.95) for those known to be on lipid-lowering treatment.

By 12 years after initial stroke, 376 stroke recurrences had occurred. Again, a decrease in hazard ratios were reported but only the use of statins and other agents to reduce hypercholesterolaemia at any time point during follow-up showed was shown to

decrease the risk of stroke recurrence for all stroke subtypes (HR 0.56 95%CI 0.35-0.91; p=0.05), as well as for ischaemic strokes only (HR 0.60 95%CI 0.37-0.99; p=0.04).

Conclusions -The results demonstrate reduction in stroke recurrence risk at both 5 and 12 years when lipid-lowering medications were used in the treatment of hypercholesterolaemia. Non-significant decreasing trends in risk of stroke recurrence were also noted in patients using anti-hypertensive and anticoagulant medication to treat diagnoses of hypertension and atrial fibrillation up to five and 12 years after first stroke, therefore type 2 error cannot be excluded.

6.1 Background

Knowing when a recurrent stroke is most like to occur, and what its subtype is likely to be, provides clinicians with useful information when planning treatment, particularly secondary prevention plans for patients after a first or subsequent recurrent stroke.

Risk factors which develop after a first stroke, also require management in a similar fashion. For example, an individual may have repeated normal blood pressure readings at the time of their first stroke, and therefore not be diagnosed with high blood pressure and not require anti-hypertensive medication. During routine follow-up with their GP three years later, they may be found to be hypertensive and started on appropriate medication.

As described in Chapter 1 of this thesis, there are many effective secondary prevention interventions available for stroke patients with the aim of reducing the risk of stroke recurrence, however population-based data on the effectiveness of this on reducing stroke recurrence risk is lacking. This is particularly important as both UK and European time-trends indicate that more patients have been prescribed medications to control cardiovascular risk factors over the last decade than previously, and stroke patients may remain on these medications for many years[160, 166].

Most studies estimating risk reduction estimate cardiovascular risk and are not powered for a primary stroke-specific endpoint, and certainly not an endpoint for stroke recurrence, due to factors included small numbers of participants, choice of population studied, and the choice of study design used[167].

In the Heart Protection Study, 3280 patients with a previous stroke and 17256 with previous vascular disease or diabetes were randomly allocated 40 mg simvastatin daily or a matched placebo. Whilst the investigators found that patients with a previous stroke had no reduction in stroke recurrence rate, a significant 20% (8–29%) reduction in the rate of any major vascular event (defined as non-fatal myocardial infarction, coronary death, stroke of any type, and coronary or non-coronary revascularisation) was noted during the 5 year study period[168].

As described in Chapter 1, The Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) study investigated the effect of aggressive atorvastatin therapy (80mg/day) on patients who had a previous TIA or stroke, had a low-density lipoprotein (LDL) level between 100 mg/dl and 190 mg/dl (2.58-4.91mmol/l) and had no evidence of coronary artery disease. Patients were followed up for 6 years and a 16% risk reduction in time to stroke was demonstrated in the atorvastatin group, compared to the control group as well as a 35% reduction in coronary events. However as mentioned earlier in this thesis, a 66% increased risk of intra-cerebral haemorrhage was found in the atorvastatin group[64].

A recent article by Hankey in 2014, reviewed the evidence for selected secondary prevention medications and interventions to reduce the risk of stroke recurrence both in the short and long-term period[169]. The review highlights the importance of timing when initiating antiplatelet and anticoagulant medications after first stroke. Sandercock *et al* in 2008 conducted a systematic review and meta-analysis of over 40000 patients given aspirin 160-300mg daily 48 hours after first stroke and continuing for a period of two to four weeks. They found that during the six months follow-up period, the odds of

recurrent ischaemic stroke reduced by 23% (OR 0.77, 95%CI 0.69-0.87); and the odds of any recurrent stroke reduced by 12% (OR 0.88, 95%CI 0.79-0.97). However the odds of symptomatic intracranial haemorrhage increased by 22% during the study period (OR 1.22 95%CI 1.00-1.50)[170].

Similarly, another systematic review by Sandercock investigating patients with acute ischaemic stroke of cardiac or arterial origin found that anticoagulation started within 48 hours of stroke had no effect on the risk of early ischaemic stroke (OR 0.85, 95%CI 0.66-1.09) but substantially increased the risk of intracranial haemorrhage (OR 2.55 95%CI 1.19-5.45). These results were independent of the type of anticoagulant used, and patient's susceptibility to both thrombotic and haemorrhagic events[171].

In the longer term, the benefits of anticoagulant and antiplatelet medications in reducing the risk of stroke recurrence is more evident in the randomised control trial setting. As described in Chapter 1, large studies such as the second European Stroke Prevention Study (ESPS-2), and the CAPRIE and MATCH trial have demonstrated a decrease in risk of stroke recurrence conveyed by the use of antiplatelet medications[52, 53, 55]. Similarly the European Atrial Fibrillation Trial demonstrated the benefits of warfarin on risk of stroke recurrence in patients with atrial fibrillation, provided patients did not have a known contraindication to the use of warfarin[57].

The effect of anti-hypertensive medication on the risk of stroke recurrence is less clear, even when comparing the results of randomised control trials. As demonstrated in the PROGRESS study, comparing a perindopril-based blood pressure lowering regimen in individuals with a previous stroke or TIA, both hypertensive and non-hypertensive patients noted a 25% reduction in risk in stroke recurrence over the 4 year follow-up period[49]. Hypertension is widely considered one of the most important stroke risk factors, and was cited as being responsible for up to 35% of the population attributable risk of stroke in the INTERSTROKE multi-centre case-control study. Further research is clearly needed to understand the association between management of this common risk

factor and risk of stroke recurrence, and to reduce the hypertension-associated burden of stroke and stroke recurrence [172].

Inequalities in the use of appropriate primary and secondary prevention medications between different patient groups still exist[173]. However, despite these differences, it remains unclear how the association between secondary prevention medications and risk of stroke recurrence translates to population-based cohorts. Therefore, this chapter estimates the association between use of secondary prevention medication (anti-hypertensive medication, anticoagulants, lipid-lowering, and antiplatelet agents) and risk of stroke recurrence up to 12 years after initial stroke in the population-based South London Stroke Register.

6.2 Methods

The use of the SLSR as the study population, the case ascertainment and data collection methods used in this chapter have previously been detailed in Chapter 2.

6.2.1 Variable definition

With the exception of the variables related to the use of secondary prevention, the main explanatory and outcome variables used in this study have been defined previously in this thesis.

The four additional variables used in this study map the use of anti-hypertensive, anticoagulant, lipid-lowering, and antiplatelet medications during the study period. These variables were created by categorising the different classes of anti-hypertensive, lipid-lowering, anticoagulant and antiplatelet medications prescribed to SLSR patients during the study period. A complete list of the classes of medications categorised within

each variable can be found in Appendix 5. The categories of these variables used are described in Table 23.

Variable	Categories
Hypertension	No hypertension Hypertension diagnosed – no treatment Hypertension diagnosed - on treatment Hypertension diagnosed - unknown treatment Hypertension status unknown
Statin	No hypercholesterolaemia Hypercholesterolaemia - no treatment Hypercholesterolaemia diagnosed - on treatment Hypercholesterolaemia diagnosed - unknown treatment Hypercholesterolaemia status unknown
Anticoagulation	No atrial fibrillation Atrial fibrillation diagnosed - no treatment Atrial fibrillation – on treatment Atrial fibrillation – unknown treatment Atrial fibrillation status unknown
Antiplatelet	No antiplatelet medication On antiplatelet medication Antiplatelet medication status unknown

Table 23. Time-dependent variables

These variables were derived using data collected as part of the initial and annual follow-up interviews at the SLSR as well as at the time of stroke recurrence. At each time point, questions enquiring about a past medical history or recent diagnosis of hypertension, high cholesterol and atrial fibrillation were asked to the SLSR participant or their relative by the fieldworker conducting the interview. Additionally, a full list of all medication taken was obtained from the own patient's pharmacy medication list or from the GP if the list was not available. The full list of questions asked at both initial and annual follow-up can be found in Appendix 2. It is important to note that the questions regarding a diagnosis of hypercholesterolaemia, or the use of medication to treat the condition, was only routinely collected at the South London Stroke Register from 1999.

The generation of these time-dependent variables shall be discussed further in Section 6.2.2.

6.2.2 Statistical methods

Time-dependent covariates were constructed to represent change in use of anti-hypertensive, anticoagulant, lipid-lowering and antiplatelet medications using the programming statement method in SAS.

The SAS statistical package was used in order to undertake these analyses at the advice of my PhD supervisor Professor Andy Grieve. The SAS programming statement method was used as the dataset only included one record for each individual and therefore the time-varying covariates were defined within the programming statements[174]. Whilst this allowed the time-dependent covariates to be created as outlined below, multivariable time-dependent Weibull proportional hazard models were unable to be constructed, therefore Cox proportional hazards models were used to undertake the analyses in this chapter. As mentioned earlier in this thesis, Cox Proportional Hazards models make no assumption about the form the underlying hazard of stroke recurrence takes and therefore are suitable to be used as a proxy in these analyses[125].

Indicator variables were created to represent the covariate changes, as the time-dependent covariates in this study have potential to move between categories more than once. For example, someone known at a certain time-point to be on medication for hypertension may have the medication discontinued at a later time-point for a variety of reasons. Output records were then created for each time-period at which a covariate remains constant using DO statement loops from the first time-period (at 3 months) until the end of the study period (12 years after first stroke).

Multivariable time-dependent Cox proportional hazard models were constructed using the PROC PH Reg application of SAS version 9.2. ARRAY statements were used to introduce the different covariate categories and assignment statements were used to define the time-varying covariates[174, 175]. Cox proportional hazard models were

therefore used to estimate the effect of time-dependent risk factor modification on the risk of stroke recurrence up to 12 years after first stroke in the SLSR population. Subset analyses were conducted to estimate the effect on patients with a first ischaemic stroke only.

Studies by Peduzzi et al, have previously investigated the effect of differing events per independent variable (EPV) on proportional hazards regression analysis using Monte Carlo simulation techniques on data from randomised control trials[176]. Their studies found that whilst a single figure cut-off figure was difficult to set, an EPV of 10 or greater was not associated with significant bias or precision issues in the results reported. [176-178]. The studies reported in this chapter were designed to maintain an EPV of approximately 10.

6.3 Results

6.3.1 Demographic data

The prior-to-stroke characteristics of the study population were described in Section 5.3.1 and are summarised in Table 16 (taken from Section 5.3.1). The number of patients included the both the full study analyses as well as the ischaemic stroke only subset analyses, during the 12 year study period are summarised in Table 24. The number of participants remaining in the study throughout the study period by covariate, can be found in Appendix 6.

	Total, N(%)
Total	4023
Age group	
<65	1248 (31)
65-74	1041 (26)
75-84	1734 (43)
Gender	
Male	2024 (50)
Ethnicity	
White	2890 (72)
Black	805 (20)
Other	225 (5.6)
Socio economic status	
Non-manual	1082 (26)
Manual	2148 (53)
Economically inactive	562 (14)
Unknown	221 (5.5)
Prior to stroke risk factors	
Previous TIA	472 (12)
Hypertension	2436 (61)
Diabetes Mellitus	712 (18)
Previous MI	415 (10)
Atrial Fibrillation	629 (16)
Smoker or ex-smoker	2404 (60)

Table 16. Demographic data

Time after first stroke	Number at start of time period	Number with stroke recurrence	Number censored - died	Number censored – at last follow-up	Number in study at end of time-period
All strokes					
0-1 years	4023	191 (4.7%)	688 (16.9%)	891 (22.2%)	2253 (56.0%)
1- 5 years	2253	149 (6.6%)	290 (12.9%)	824 (36.6%)	990 (43.9%)
5-12 years	990	53 (5.4%)	165 (16.7%)	660 (66.7%)	112 (11.3%)
Ischaemic strokes only					
0-1 years	3293	162 (4.9%)	503 (15.3%)	709 (21.5%)	1919 (58.3%)
1- 5 years	1919	130 (6.8%)	263 (13.7%)	724 (37.7%)	802 (41.8%)
5-12 years	802	47 (5.7%)	146 (18.2%)	526 (65.6%)	83 (10.3%)

Table 24. The number of participants in the study during the study period

6.3.2 The effect of time-dependent risk factor modification on the risk of stroke recurrence after first stroke

The effect of the time-dependent variables on the risk of stroke recurrence up to 5 years after first stroke, adjusted for key socio-demographic and prior-to-stroke risk factors are

shown in Table 25. The results are displayed for all stroke patients as well as for patients with an ischaemic first stroke only.

At 5 years after initial stroke, 322 recurrent strokes were recorded, with the number decreasing to 276 recurrences when only ischaemic first strokes were considered. When all stroke subtypes were included, it was notable that there was a general decrease in the hazard ratios estimating risk of stroke recurrence when patients were on anti-hypertensive, lipid-lowering and anticoagulant medications compared to having a diagnosis of the relevant conditions but not on medication. The hazard ratios for hypercholesteriolaemia were shown to decrease from 1.46 (95%CI 0.82-2.60) for those not on treatment, to 0.57 (0.34-0.95) for those known to be on lipid-lowering treatment. However, these results did not show statistical significance and the related 95% Confidence Intervals were found to be wide. Similar results were noted when only participants with an ischaemic first stroke subtype were analysed.

12 years after an initial stroke, 376 stroke recurrences were recorded (322 recurrences when only ischaemic first strokes were analysed). When both patients with all stroke subtypes as well as those with ischaemic strokes only were analysed, a general non-significant decrease in hazard ratios was found for patients on anti-hypertensive, lipid-lowering, and anticoagulant medications compared to those with a diagnosis of hypertension, hypercholesterolaemia and AF who were not on medication. Again the hazard ratio was shown to be considerable, i.e. the hazard ratio for patients with atrial fibrillation not on treatment was estimated to be 1.55 (95%CI 1.00-2.43) reducing to 1.29 (95%CI 0.56-2.96) when patients were on treatment.

The use of statins and other agents to reduce hypercholesterolaemia showed statistical significance for both all stroke subtypes (p=0.05) and for ischaemic strokes categories only (p=0.04). The effect of the four time-dependent variables on risk of recurrence up to 12 years after first stroke is shown in Table 26

As requested in the revisions to this thesis, the time–dependent variables were re-parameterised using the untreated condition as the baseline comparator value. For example, for the hypertension variable, 'Hypertension- no treatment' was used as the baseline variable. Estimates relating to the use of antiplatelet medication were not re-parameterised as they were not linked to a specific cardiovascular risk factor in the original analyses. All other covariates were entered into the multivariable model unchanged.

The re-parameterised time-dependent covariates estimated up to 5 years after first stroke are presented in Table 27, estimates up to 12 years are presented in Table 28. A substantial reduction stroke recurrence risk can be observed in individuals with hypercholesterolaemia on treatment compared to those who not on treatment. This risk reduction was estimated at time-points up to both 5 years (HR 0.39 95%CI 0.19-0.80; HR 0.35 95% CI 0.18-0.74) and 12 years after first stroke (HR 0.37 95%CI 0.17-0.73; HR 0.34 95%CI 0.17-0.67) for those with all stroke subtypes and ischaemic strokes respectively.

	All strokes		Ischaemic strokes only	
	HR (95%CI)	P value	HR (95%CI)	P value
Age group				
<65	1	0.005	1	0.005
65-74	1.11(0.82-1.49)		1.06(0.79-1.42)	
>75	1.55(1.17-2.04)		1.56(1.18-2.06)	
Ethnicity				
White	1	0.273	1	0.206
Black	1.24(0.95-1.62)		1.24(0.95-1.62)	
Other	0.95(0.58-1.54)		0.78(0.48-1.27)	
Gender				
Male	1	0.948	1	0.933
Female	1.01(0.81-1.26)		0.93(0.75-1.17)	
Prior-to-stroke risk factors				
No TIA	1	0.009	1	0.004
TIA	1.47(1.10-1.97)		1.56(1.17-2.08)	
No MI	1	0.018	1	0.009
MI	1.48(1.07-2.04)		1.55(1.12-2.14)	
No Diabetes Mellitus	1		1	0.384
Diabetes Mellitus	1.15(0.89-1.48)	0.275	1.13(0.88-1.45)	
Time-dependent risk factors				
No hypertension	1	0.617	1	0.553
Hypertension – no treatment	1.27(0.83-1.93)		1.29(0.81-2.05)	
Hypertension –on treatment	1.03(0.73-1.46)		1.08(0.77-1.52)	
Hypertension – unknown treatment	0.53(0.12-2.37)		0.60(0.13-2.66)	
Hypertension status unknown	0.85(0.52-1.39)		0.76(0.46-1.24)	
No hypercholesterolaemia	1	0.105	1	0.083
Hypercholesterolaemia, no treatment	1.46(0.82-2.60)		1.71(0.96-3.04)	
Hypercholesterolaemia, on treatment	0.57(0.34-0.95)		0.61(0.36-1.01)	

Hypercholesterolaemia, unknown treatment	1.25(0.17-9.07)		1.51(0.21-10.98)	
Hypercholesterolaemia status unknown	0.99(0.69-1.44)		1.09(0.75-1.58)	
No antiplatelet medication	1	0.328	1	0.287
On antiplatelet medication	0.99(0.75-1.30)		0.90(0.69-1.19)	
Antiplatelet medication status unknown	1.32(0.88-1.99)		1.28(0.85-1.92)	
No AF	1	0.469	1	0.33
AF diagnosed, no treatment	1.53(0.96-2.45)		1.64(1.03-2.61)	
AF diagnosed, on treatment	1.16(0.47-2.87)		0.74(0.30-1.83)	
AF diagnosed, unknown treatment	1.08(0.13-8.72)		1.36(0.17-10.98)	
AF status unknown	1.23(0.81-1.87)		1.23(0.81-1.87)	

Table 25 The effect of risk factor management on the risk of stroke recurrence in a) all stroke patients b) patients with an ischaemic stroke only, up to 5 years after first stroke.

	All Strokes		Ischaemic strokes only	
	HR (95%CI)	P value	HR (95%CI)	P value
Age group				
<65	1	<0.001	1	0.001
65-74	1.36(1.04-1.77)		1.31(0.97-1.76)	
>75	1.68(1.29-2.18)		1.70(1.28-2.26)	
Ethnicity				
White	1	0.309	1	0.238
Black	1.20(0.94-1.55)		1.21(0.92-1.59)	
Other	0.94(0.60-1.48)		0.81(0.48-1.37)	
Gender				
Male	1	0.948	1	0.946
Female	0.99(0.81-1.22)		0.95(0.76-1.18)	
Prior-to-stroke risk factors				
No TIA	1	0.036	1	0.022
TIA	1.34(1.02-1.76)		1.40(1.05-1.86)	
No MI	1	0.011	1	0.005
MI	1.48(1.10-2.00)		1.55(1.14-2.11)	
No Diabetes Mellitus	1	0.275	1	0.349
Diabetes Mellitus	1.14(0.90-1.44)		1.13(0.88-1.45)	
Time-dependent risk factors				
No hypertension	1	0.79	1	0.834
Hypertension – no treatment	1.21(0.80-1.83)		1.23(0.78-1.94)	
Hypertension –on treatment	1.05(0.75-1.45)		1.10(0.77-1.57)	
Hypertension – unknown treatment	0.55(0.13-2.42)		0.61(0.14-2.73)	
Hypertension status unknown	1.05(0.66-1.66)		0.98(0.60-1.61)	
No hypercholesterolaemia	1	0.05	1	0.041
Hypercholesterolaemia, no treatment	1.51(0.88-2.60)		1.78(1.03-3.07)	
Hypercholesterolaemia, on treatment	0.56(0.35-0.91)		0.60(0.37-0.99)	

Hypercholesterolaemia, unknown treatment	1.13(0.38-20.00)		1.38(1.19-10.2)	
Hypercholesterolaemia status unknown	0.95(0.83-1.74)		1.05(0.71-1.55)	
No antiplatelet medication	1	0.583	1	0.639
On antiplatelet medication	1.22(0.84-1.77)		0.98(0.73-1.31)	
Antiplatelet medication status unknown	1.55(1.00-2.43)		1.17(0.78-1.77)	
No AF	1	0.336	1	0.093
AF diagnosed, no treatment	1.55(1.00-2.43)		1.65(1.04-2.62)	
AF diagnosed, on treatment	1.29(0.56-2.96)		0.90(0.33-2.48)	
AF diagnosed, unknown treatment	1.05(0.13-8.38)		1.30(0.16-10.73)	
AF status unknown	1.27(0.86-1.90)		1.22(0.80-1.87)	

Table 26 The effect of risk factor management on the risk of stroke recurrence in a) all stroke patients b) patients with an ischaemic stroke only, up to 12 years after first stroke.

	All Strokes		Ischaemic strokes only	
	HR (95%CI)	P value	HR (95%CI)	P value
Time-dependent risk factors				
Hypertension – no treatment	1	0.617	1	0.553
No hypertension	0.79 (0.52-1.21)		0.78 (0.55-1.28)	
Hypertension –on treatment	0.82 (0.53-1.26)		0.84 (0.55-1.29)	
Hypertension – unknown treatment	0.42 (0.09-1.93)		0.47 (0.05-0.98)	
Hypertension status unknown	0.67 (0.37-1.22)		0.59 (0.40-1.29)	
Hypercholesterolaemia, no treatment	1	0.105	1	0.083
No hypercholesterolaemia	0.69 (0.39-1.22)		0.59 (0.35-1.08)	
Hypercholesterolaemia, on treatment	0.39 (0.19-0.80)		0.35 (0.18-0.74)	
Hypercholesterolaemia, unknown treatment	0.86 (0.11-6.68)		0.90 (0.11-6.47)	
Hypercholesterolaemia status unknown	0.68 (0.36-1.28)		0.64 (0.35-1.20)	
No antiplatelet medication*	1	0.328	1	0.287
On antiplatelet medication	0.99(0.75-1.30)		0.90(0.69-1.19)	
Antiplatelet medication status unknown	1.32(0.88-1.99)		1.28(0.85-1.92)	
AF diagnosed, no treatment	1	0.469	1	0.33
No AF	0.62 (0.39-0.98)		0.58 (0.41-1.02)	
AF diagnosed, on treatment	0.72 (0.27-1.94)		0.43 (0.29-2.11)	
AF diagnosed, unknown treatment	0.68 (0.08-5.65)		0.79 (0.09-5.75)	
AF status unknown	0.76 (0.43-1.37)		0.71 (0.40-1.28)	

Table 27 Reparameterisation of the time-dependent variables displayed in Table 25 showing the effect of risk factor management on the risk of stroke recurrence up to 5 years after first stroke.

* The estimates for the Antiplatelet medication covariate are presented unchanged. All other estimates presented in Table 25 remain unchanged.

	All Strokes		Ischaemic strokes only	
	HR (95%CI)	P value	HR (95%CI)	P value
Time-dependent risk factors				
Hypertension – no treatment	1	0.79	1	0.834
No hypertension	0.83 (0.55-1.26)		0.82 (0.52-1.29)	
Hypertension –on treatment	0.87 (0.57-1.32)		0.90 (0.56-1.42)	
Hypertension – unknown treatment	0.46 (0.10-2.06)		0.50 (0.11-2.31)	
Hypertension status unknown	0.87 (0.49-1.52)		0.80 (0.43-1.48)	
Hypercholesterolaemia, no treatment	1	0.05	1	0.041
No hypercholesterolaemia	0.66 (0.39-1.14)		0.56 (0.33-0.97)	
Hypercholesterolaemia, on treatment	0.37 (0.19-0.73)		0.34 (0.17-0.67)	
Hypercholesterolaemia, unknown treatment	0.75 (0.10-5.76)		0.78 (0.10-6.11)	
Hypercholesterolaemia status unknown	0.63 (0.34-1.13)		0.59 (0.32-1.09)	
No antiplatelet medication*	1	0.583	1	0.639
On antiplatelet medication	1.22(0.84-1.77)		0.98(0.73-1.31)	
Antiplatelet medication status unknown	1.55(1.00-2.43)		1.17(0.78-1.77)	
AF diagnosed, no treatment	1	0.336	1	0.093
No AF	0.62 (0.40-0.95)		0.58 (0.37-0.91)	
AF diagnosed, on treatment	0.80 (0.32-1.99)		0.52 (0.18-1.55)	
AF diagnosed, unknown treatment	0.65 (0.08-5.38)		0.76 (0.09-6.46)	
AF status unknown	0.79 (0.45-1.37)		0.71 (0.40-1.26)	

Table 28 Reparameterisation of the time-dependent variables displayed in Table 26 showing the effect of risk factor management on the risk of stroke recurrence up to 12 years after first stroke.

* The estimates for the Antiplatelet medication covariate are presented unchanged. All other estimates presented in Table 26 remain unchanged.

6.4 Discussion

This chapter investigated the association between the use of four widely used secondary prevention measures (anti-hypertensive medication, lipid-lowering medication; antiplatelet agents and anticoagulants) and risk of stroke recurrence at five and 12 years after first stroke. The results demonstrate a decreasing hazard of risk of stroke recurrence in patients using anti-hypertensive, lipid-lowering and anticoagulant medication, compared to those with diagnoses of hypertension, hypercholesterolaemia and AF not taking medication during both the five and 12 year time-periods. The use of statins and other anti-cholesterol medication had the largest effect on reducing the risk of stroke recurrence. with statistical significance noted across the hypercholesterolaemia categories throughout the time-period analysed for both all stroke subtypes and ischaemic strokes only.

Analyses described in Chapter 3 of this thesis highlight the importance of cardiovascular risk factors as predictors of stroke recurrence up to 10 years after first stroke within the South London population. Atrial fibrillation and myocardial infarction were estimated to increase the risk of stroke recurrence throughout the time period analysed, and a previous diagnosis of hypertension was identified as a predictor of stroke recurrence up to 5 and 10 years after first stroke. The overlapping confidence intervals in the analyses in Chapter 3, demonstrated throughout the 10 year time period, indicate that cardiovascular risk factors, in particular hypertension, atrial fibrillation and a previous history of myocardial infarction, may be predictors of stroke recurrence throughout the study period and have failed to gain significance due to Type 2 error.

As described previously, there is no consensus in previous literature regarding predictors for stroke recurrence beyond 1 year with a past history of hypertension reported as a predictor of recurrence up to 5 years, and a history of diabetes reported up to 10 years after first stroke [17, 97, 104, 105]. In Chapter 1 of this thesis, it was hypothesised that *'the treatment of modifiable predictors of stroke recurrence, at the appropriate time point after stroke recurrence, will reduce the risk of stroke recurrence'.*

On the basis of the results described in Chapter 3 as well as the predictors outlined in the previous literature, it is therefore surprising that, in these analyses, only the hypercholesterolaemia covariate supports this hypothesis.

One reason could be due to the small sample size. As demonstrated in Table 24, the number of participants with a stroke recurrence at each time-point, decreased throughout the study period and by the end of the time-period very small numbers of participants had a stroke recurrence. The small sample size reduces power and could lead to a type 2 error whereby a real difference was missed.

As with any longitudinal study, the loss of participants during the follow-up period is common. As the sensitivity analyses undertaken in Chapter 3 found similar results when and imputed dataset was used compared to the main analyses further multiple imputation was not undertaken as part of this thesis. As yet unpublished analyses undertaken at the SLSR found baseline stroke severity indicators to be important predictors of being lost-to-follow-up. Associations between stroke severity markers and the development and subsequent treatment of cardiovascular risk factors has not been extensively covered in the published literature so this may be an area for further work to be focused outside of this thesis.

Tables indicating the number of participants remaining in the study, by covariate, are displayed in Appendix 6. As mentioned earlier in this chapter, the variables related to hypercholesterolaemia, used to derive the time-dependent covariate, were only collected by the SLSR from 1999 onwards so this variable was missing in participants from the earlier years of the SLSR. As analyses still indicated that medication to treat hypercholesterolaemia reduced the risk of stroke recurrence up to 5 and 12 years after first stroke it may be the case that due to the small sample size a smaller effect size has been noted in these analyses, due to type 2 error. This may also be the case for the treatment of atrial fibrillation variable as when the estimates were re-parameterised, the hazard ratios both up to 5 years and 12 years indicated a potential risk reduction in stroke recurrence however the estimated 95% confidence intervals were wide (HR 0.72

(95%CI 0.27-1.94) up to 5 years for all strokes; HR 0.43 (95%CI 0.29-2.11) up to 5 years for ischaemic strokes only; HR 0.80 (95% 0.32-1.99) up to 12 years for all strokes; HR 0.52 (95% 0.18-1.55) up to 12 years for ischaemic strokes only.

As described above, the hazard ratios estimated for hypertension, hypercholesterolaemia and AF show decreasing hazard ratios when secondary prevention is used at both five and 12 years after first stroke and the 95% confidence intervals were wide-ranging. Whilst the analyses in this chapter maintain an events per variable ratio (EPV) equal to or greater than 10 with the exception of the risk of recurrence up to 5 years for ischaemic stroke only analyses which have an EPV of 8.5, the EPV range was at the lower end of the acceptable range of values. It has been described by Peduzzi *et al* that low EPV can lead to conservative tests being carried out, with the null hypothesis being rejected less often than the stated significance level, leading to a type 2 error[178].

For this reason, analyses were not carried out to estimate the effect of secondary prevention on the risk of recurrence up to one year after first stroke. 190 stroke recurrences were reported during this time period leading to the number of events per variable falling below 6. One way of mitigating against a low number of events per variable could be by reducing the number of categories for each secondary prevention variable. In these analyses, two 'unknown' variables were used distinguishing between those known to have the condition, for example hypertension, but not known if they were on medication, from those for whom no information was available regarding their hypertension status. The wide confidence intervals for these missing data categories indicate small numbers in these groups which could be masking the true effect of these secondary prevention variables and risk of stroke recurrence. Therefore combining these groups for future analyses should be considered

The use of time-dependent variables enables the development and treatment of cardiovascular risk factors throughout the follow-up period for to be taken into account in study analyses. However secondary prevention use is largely self-reported at the

SLSR. Verification of medication by the GP of the participant gives a record of what an individual should be taking. As discussed in Chapter 1, compliance can be a serious issue.

A study looking at factors associated with medication non-persistence six and 12 months after stroke by Lummis *et al* in Canada, found that in particular for anticoagulant medications, younger patients were less likely to discontinue medication than those aged 80 years or more (OR 0.23, 95% CI 0.06-0.81), and people who were considered disabled before admission were more likely to be discontinue medications than those not disabled (OR 7.01, 95% CI 1.66-29.58)[175]. Another Canadian study by Tsai *et al* found that the provision of a prescription to stroke patients strengthens adherence one week after discharge for both prior and new users of both anti-hypertensive and lipid-lowering drugs. This was particularly important as the authors found medication adherence one week after discharge for acute ischaemic stroke predicted adherence for secondary preventive therapies at 1 and 2 years highlighting the importance of early compliance amongst these patients [179].

The capture-recapture system used at the SLSR, coupled with the algorithm described in the Chapter 2 of this thesis used to identify any previously unrecorded stroke recurrences from ONS data, reduce the risk of 'missed' stroke recurrences. However the data collected by the SLSR does not account for those who died from causes not related to their initial or a subsequent stroke, who may have gone on to have a second stroke if they had not died. The results presented in this chapter may therefore under-estimate the true effect of secondary protection on risk of stroke recurrence if this group of SLSR participants were taken into account. The effect of stroke recurrence on the risk of death after initial stroke, and in particular the association between stroke recurrence and death, will be explored in more detail in Chapter 7.

Whilst it appears likely that the methodological factors described above have a key role in the hazard ratios demonstrating a decreasing trend, but not reaching statistical significance, the possibility remains that the results demonstrated in this chapter may be

the true result. One explanation could be that whilst the cardiovascular risk factors tested in this chapter were demonstrated in Chapter 3 to be important predictors of increased recurrence risk, the management of other risk factors may more important for certain aetiological stroke subtypes. Large artery atherosclerosis has been shown to be an important cause of transient ischaemic attacks, and if the stenosis is severe, carotid revascularisation may be performed to reduce the stenosis[134]. Future research conducted should include the association of carotid revascularisation on risk of stroke recurrence.

The SLSR dataset used for these analyses covers a wide time-period, since 1995, during which time the primary and secondary prevention used in stroke care has changed considerably. Univariate analyses described in Chapter 5 estimate the cumulative risk of stroke recurrence one year after initial stroke to have decreased from 8.2% in 1995-1999, to 6.4% in 2000-2004,and to 5.0% from 2005-2009 (Table 18). Better management of all stroke patients due to measures such as the prompt use of thrombolytic agents, stroke unit admissions and the aggressive risk factor management of patients with secondary prevention medication such as anti-hypertensive and anticoagulant medications may have reduced the risk of stroke recurrence for all patients in this study. Further analyses stratified by year of stroke for different time period (i.e.) 1995-1999; 2000-2004; 2005-2009, or by including year of stroke as a covariate in the time-dependent model could help to understand the effect of temporal differences in stroke care.

6.5 Summary

In conclusion, this chapter uses time-dependent survival analyses to provide long-term estimates of the effect of commonly used secondary prevention medication on the risk of stroke recurrence up to 12 years after first stroke. The results demonstrate reduction in stroke recurrence risk at both 5 and 12 years when lipid-lowering medications were used in the treatment of hypercholesterolaemia, and non significant decreasing trends in risk of stroke recurrence in patients using anti-hypertensive and anticoagulant

medication to treat diagnoses of hypertension and atrial fibrillation during both the five and 12 year time-periods.

Lack of statistical significance demonstrated may be due to Type 2 error caused by methodological issues e.g. small number of events at annual time points measured, rather than due to a lack of clinical significance. Temporal differences in the management of stroke patients since the SLSR began should also be considered in further analyses.

The effect of stroke recurrence on the risk of death after initial stroke, and in particular associations between stroke recurrence and death in the time-period after an initial stroke needs to be considered further. This will be explored in more detail in Chapter 7.

Chapter 7 The effect of stroke recurrence on risk of death after first-ever stroke

Abstract

Background – Data estimating the association between stroke recurrence and risk of death after first stroke, and in particular taking into account the association between stroke recurrence and death are lacking. Furthermore it is unclear whether a critical time-period during which a stroke recurrence has a greater effect on risk of death can be identified.

Methods – Kaplan-Meier estimates and stratified Cox proportional hazards models were used to assess the effect of stroke recurrence on risk of death 1, 5, 10 and 15 years after first stroke in SLSR patients. Adjustment in multivariable analyses included socio-demographic factors, stroke subtype, case-mix, prior-to-stroke risk factors, process of care and time-dependent variables. Stroke recurrence was constructed as a time-dependent covariate in the multivariable analyses, using STATA to split the dataset at time of stroke recurrence.

Results - Between January 1995 and December 2011, 4478 patients with first-ever stroke were registered at the SLSR. The mean follow-up time was 4.03 years, with 18025.81 person years of follow-up included. During this period, 395 recurrent strokes were documented. The risk of death 1, 5, 10 and 15 years after initial stroke was 31.7% (95% CI 30.3 to 33.1%), 52.9% (95% CI 51.4 to 54.5%), 70.2% (95% CI 68.5 to 71.8%) and 81.6% (95%CI 79.6 to 83.5%) respectively. Stroke recurrence was found to be significantly associated with an increase the risk of death at all time points analysed and was therefore considered to be a predictor. When stroke recurrence was categorised according to the time-point the recurrence took place, increased risk was found at all time-points analysed, up to 15 years after first stroke. Stroke recurrence within the first year after the initial stroke was particularly associated with increased risk of death at all time points. The 1 year risk of death was estimated to be over five times higher in those with a stroke recurrence by 3 months (HR 5.45(95%CI 3.46-8.59%), and eight time

higher in those with a stroke recurrence by 1 year (HR 8.08(95%CI 5.27-12.4%) compared to those without a stroke recurrence.

Conclusions -This study demonstrates that increased risk of death associated with stroke recurrence during the first year after first stroke, is maintained up to 15 years. This identifies the first year after stroke as a critical time-period for targeted risk factor management. Further work is needed to improve methods of identification of those at greatest risk of early stroke recurrence.

7.1 Background

Knowledge of a patient's long-term prognosis for survival after a stroke is important to both patients and their clinicians. Prognostic information can help aid the selection of appropriate treatments for the patient and facilitate the provision of accurate information to the patient and their family [27].

Despite indications that survival post-stroke is improving, stroke survivors remain at an increased risk of death after first stroke. Both Aarnio *et al,* who studied 30 day survivors of first-ever ischaemic stroke aged 15-49 years in Finland, and Rutten-Jacobs *et al*, who investigated mortality and cause of death after acute stroke in adults aged 18-50 years in the Netherlands, found the observed risk of mortality to be significantly higher than expected for these groups,[180, 181]. In particular, Aarnio *et al* reported mortality amongst stroke patients to be seven times higher than that for the general population matched for age, sex, calendar year and geographical area (standardised mortality ratio 6.94; 95% CI 5.84-8.04)[180].

As observed in Chapter 1 of this thesis, there is a wide variation in stroke mortality trends worldwide in particular between countries with low and declining stroke mortality rates and those with high and increasing mortality[8]. However there have been few population-based, or even hospital studies to date investigating changes in mortality

after initial stroke over time. In 2005, Hardie *et al* reported the cumulative risk of death up to 5 years after first stroke to be 59% (95%CI 53-65%) in 1989-90 and 58% (52-65%) in 1995-96 with no statistical significant improvement in survival seen between the cohorts[91]. However in a more recent hospital-based study in Taiwan, Chen *et al* reported a 1 year mortality risk reduction of 15-20% amongst patients with an ischaemic stroke and 20-25% for those with an intracranial haemorrhage when comparing the time-periods of 1997-2002 and 2003-2008 to 1991-1996[182],

As with stroke recurrence the estimates of risk of death after first stroke reported in the published literature are wide-ranging. One of the major methodological factors for the variations observed is whether studies report the risk of death at all time-points after first stroke, or whether the risk of death is reported in 30 day survivors only. The cumulative risk of death after first stroke was found to range from: 2.7% in Helsinki, Finland [183]to 28% in Copenhagen in Denmark [184]up to 1 month; from 2.4% in a multi-centre study in Japan[185] to 41% in Copenhagen up to 1 year[184]; and from 7.8% in Japan[185], to 60% in both Copenhagen, Denmark and Connecticut in the USA[184, 186] up to 5 years after first stroke.

Several stroke studies reported the risk of death for a certain group of stroke patients, for example, those with a specific stroke subtype only, or patients of a defined age-range. As described for stroke recurrence in Chapter 5 of this thesis, there has also been variation noted in risk of death estimated between different stroke subtypes. With higher death rates reported after a haemorrhagic stroke compared to an ischaemic stroke at both 30 days and 1 year after first stroke[37, 127, 182, 187], Studies have also reported differences between the aetiological stroke subtypes[139, 183, 188]. Petty *et al* reported the risk of death by five years after first stroke to be 32.2% (95% CI 21.1-43.2%) after large-artery atherosclerosis; 80.4% (95% 73.1-87.6%) after a cardio-embolic stroke; 35.1% (95% 23.6-46.0%) after a lacunar stroke, and 48.6% (95% 40.5-56.7%) after a stroke of undefined aetiology.[189].

Predictors of increasing risk of death after first stroke can be identified from the published literature. At all time points ranging from 30 days to 10 years after first stroke, older age was the most commonly reported predictor for death[27, 144, 145, 185, 190]. Cardiovascular risk-factors, such as, ischaemic heart disease, diabetes mellitus and AF recorded at the time of first stroke [127, 145, 191, 192] were also found to be consistent predictors of death, as were stroke severity markers, in particular a low GCS or urinary incontinence recorded at the time of initial stroke or during the acute phase[27, 145, 193].

Stroke recurrence has also been reported in some studies as a predictor of death after first stroke[190, 193]. It is surprising that stroke recurrence has not been implicated more often in previous literature as a key predictor of death after first stroke, as those with a stroke recurrence are known to be at higher risk of complications, and recurrent stroke has been described as a predictor of disability up to 5 years after first stroke[27].

This chapter seeks to explore the relationship between stroke recurrence and risk of death at time-points from 1 to 15 years after first stroke to ascertain the effect of stroke recurrence on death, and whether increased risk of death is dependent on the time-point after first stroke at which the stroke recurrence occurs.

7.2 Methods

7.2.1 The main variables used in multivariable analyses

Potential predictors of death after first stroke were identified through review of the literature and the following variables were selected:

Demographic factors included age (categorised as <65, 65-74, ≥75), gender, ethnicity (categorised as white, black and other) and socio-economic status. Socioeconomic status categories were grouped into non-manual (I, II, and III non-manual) or manual (III

manual, IV, and V) or economically inactive, according to the patient's current (or for the retired and others not currently working, the most recent) employment[83].

Stroke severity was defined as the presence of neurological deficit during the acute phase of the initial stroke. The level of consciousness was assessed using the Glasgow Coma Scale (GCS) dichotomized into GCS <13 (impaired consciousness) and GCS13-15 [84].

Classification of pathological stroke subtype was categorised into ischaemic stroke, PICH or SAH based on results from at least one of the following: brain imaging (CT or MRI scan) and post-mortem studies.

A range of indicators of the processes of care after an acute stroke, suggested to be useful proxy measures for the overall quality of stroke care, were examined The UK National Clinical Guidelines for Stroke published in 2012 emphasise the strong evidence in favour of specialised stroke unit care [16]. Patients were therefore classified as (1) not admitted to hospital; (2) admitted to stroke unit; (3) admitted to general medical ward/intensive care; and (4) unknown, in order for differences in risk of death related to the presence or absence of stroke unit care to be adjusted for in the analyses.

Data were also collected regarding a diagnosis of hypertension prior to first stroke, and the use of anti-hypertensive medication during the first 3 months of stroke.

7.2.2 Handling missing data

The main methods used to handle missing data in this thesis have been described in Chapter 2. Within the SLSR, reasons for missing data during follow-up include occasional retrospective registrations; patients lost to follow up either for a specific time interval i.e. missing their two year follow-up only, or indefinitely; or very rarely, due to

the patient or main carer not agreeing to being followed-up at a particular time-point. Due to the nature of the primary outcome variable and the six-monthly review of ONS records for SLSR participants who may have died, the quality of the death notifications used in this study have been considered to be accurate and up-to-date for the duration of the study period.

7.2.3 Statistical methods

Data were available from January 1 1995 and complete records were obtained up to June 30 2013. All index cases (first-ever stroke) registered up to December 31 2011 and follow-up data collected until June 30 2013 were included in analyses. Survival time was calculated from date of stroke to date of death, confirmed using ONS records. Patients with no record of death were censored 15 years after stroke.

Kaplan-Meier estimates were calculated to model the risk of death (1-survival) and therefore to measure the cumulative risk of death using Hazard Ratios (HR) and corresponding 95% confidence intervals up to 15 years after first stroke. Survival curves were constructed stratified for presence or absence of stroke recurrence, using the Kaplan-Meier method (unadjusted) and log rank tests.

Hazard ratios (HR) and the corresponding 95% confidence intervals (CI) were estimated using Cox regression analyses and the assumption of proportional hazards were assessed using log minus log survival plots.

Patients were censored if lost to follow-up, or if alive at the end of the follow-up period. In the multivariable analyses, stratified Cox Proportional Hazards Models were used to estimate the effect of stroke recurrence on the risk of death after first stroke adjusted for socio-demographic factors, stroke severity markers, cardiovascular risk factors, initial stroke subtype, process of care variables, and time-dependent factors. All analyses were conducted using STATA12 statistical package.

Stroke recurrence was constructed as a time-dependent covariate in these analyses. STATA was used to split the dataset at time of stroke recurrence, to adjust for the eventuality that an individual may die from a non-related cause before stroke recurrence, therefore not allowing a stroke recurrence to occur.

Possible interactions between ethnicity and the other explanatory variables including age, cardiovascular factors, case-mix variables, and stroke unit care, were tested by constructing interaction terms in the stratified Cox models.

7.3 Results

7.3.1 Descriptive analyses

This study included a total of 4478 first-ever stroke patients registered at the SLSR between January 1995 and December 2011. The mean follow-up time was 4.03 years, with a total of 18025.81 person years of follow-up included. During this period, 395 recurrent strokes were documented. The mean age of those included in the study was 69.9 years. Patient characteristics at time of initial stroke are presented in Table 29. The number of patients in the study at the different key time-points during the 15 year study period are summarised in Table 30. The number participants remaining in the study throughout the study period by covariate, can be found in Appendix 6.

	Total, N(%)
Total	4478
Age group	
<65	1440 (32)
65-74	1126 (25)
Gender	
Female	2210 (49)
Ethnicity	
White	3153 (72)
Black	956 (22)
Other	257 (5.9)
Socio economic status	
Non-manual	1206 (27)
Manual	2302 (51)
Unknown	274 (6.1)
Economically inactive	696 (16)
Stroke Subtype	
Infarct	3350 (81)
PICH	577 (14)
SAH	224 (5.4)
Year of initial stroke	
1995-1998	1305 (29)
1999-2002	1074 (24)
2003-2006	997 (22)
2007-2001	1102 (25)
Risk factors	
Hypertension	2724 (64)
Use of anti-hypertensives by 3 months	1194 (32)
Stroke severity Indices	
GCS <13	1201 (28)
13-15	3086 (72)
Process of care variables	
Not admitted to hospital	521 (12)
Admitted to general medical ward/ITU	1715 (38)
Admitted to Stroke Unit	2,154 (48)
Unknown	88 (2.0)

Table 29 Descriptive baseline statistics

Abbreviations: PICH Primary Intracerebral Haemorrhage, SAH Subarachnoid Haemorrhage

Time after first stroke	Number at start of time period	Number died - no recurrence	Number died - with recurrence	Number censored - no recurrence	Number censored - with recurrence	Number at end time-period– no recurrence	Number at end time-period– with recurrence
0-1 years	4478	1433 (32.0%)	63 (1.4%)	-	-	2858 (63.8%)	124 (2.8%)
1- 5 years	2982	679 (22.7%)	109 (3.6%)	505 (16.9%)	8 (0.3%)	1526 (49.7%)	156 (5.1%)
5-10 years	1682	356 (21.1%)	85 (5.1%)	525 (31.2%)	30 (1.8%)	599 (35.6%)	87 (5.2%)
10-15 years	686	103 (15.0%)	32 (4.7%)	342 (49.9%)	32 (4.7%)	148 (21.6%)	29 (4.2%)

Table 30. The number of participants remaining in the study at each during the 15 year study period

7.3.2 Survival Analyses

7.3.2.1 Univariate analyses

The cumulative risk of death up to 1 year, 5 years, 10 years and 15 years after the initial stroke were estimated to be 31.7% (95% CI 30.3 to 33.1%), 52.9% (95% CI 51.4 to 54.5%), 70.2% (95% CI 68.5 to 71.8%) and 81.6% (95%CI 79.6 to 83.5%) respectively. Table 31 displays the univariate analyses of cumulative risk of death up to 15 years for all participants, and stratified according to stroke recurrence.

	Cumulative risk of recurrence, % (95% CI)			
	By 1 year	By 5 years	By 10 years	By 15 years
All strokes	31.7 (30.3-33.1)	52.9 (51.4-54.5)	70.2 (68.5-71.8)	81.6 (79.6-83.5)
Stroke recurrence				
No recurrence	33.2 (31.7-34.7)	53.7 (52.0-55.4)	69.8 (68.0-71.6)	80.4 (78.2-82.5)
Recurrence	16.2 (12.9-20.3)	45.1 (40.2-50.2)	70.8 (65.9-75.5)	85.8 (80.9-89.9)

Table 31. Univariate analyses: cumulative risk of death after initial stroke

Figure 15 shows Kaplan-Meier plots graphically representing the survival (1-risk of death) up to 15 years after initial stroke, and survival stratified by stroke recurrence. Interestingly, Figure 15 indicates that those without a stroke recurrence are at an increased risk of death up to roughly 7 years after first stroke, after which time the lines on the Kaplan-Meier plot meet and cross-over. This is likely to be due the association between stroke recurrence and death, as an individual has to remain alive in order to be able to have a stroke recurrence. This association will be adjusted for in the multivariable analyses described in the next section.

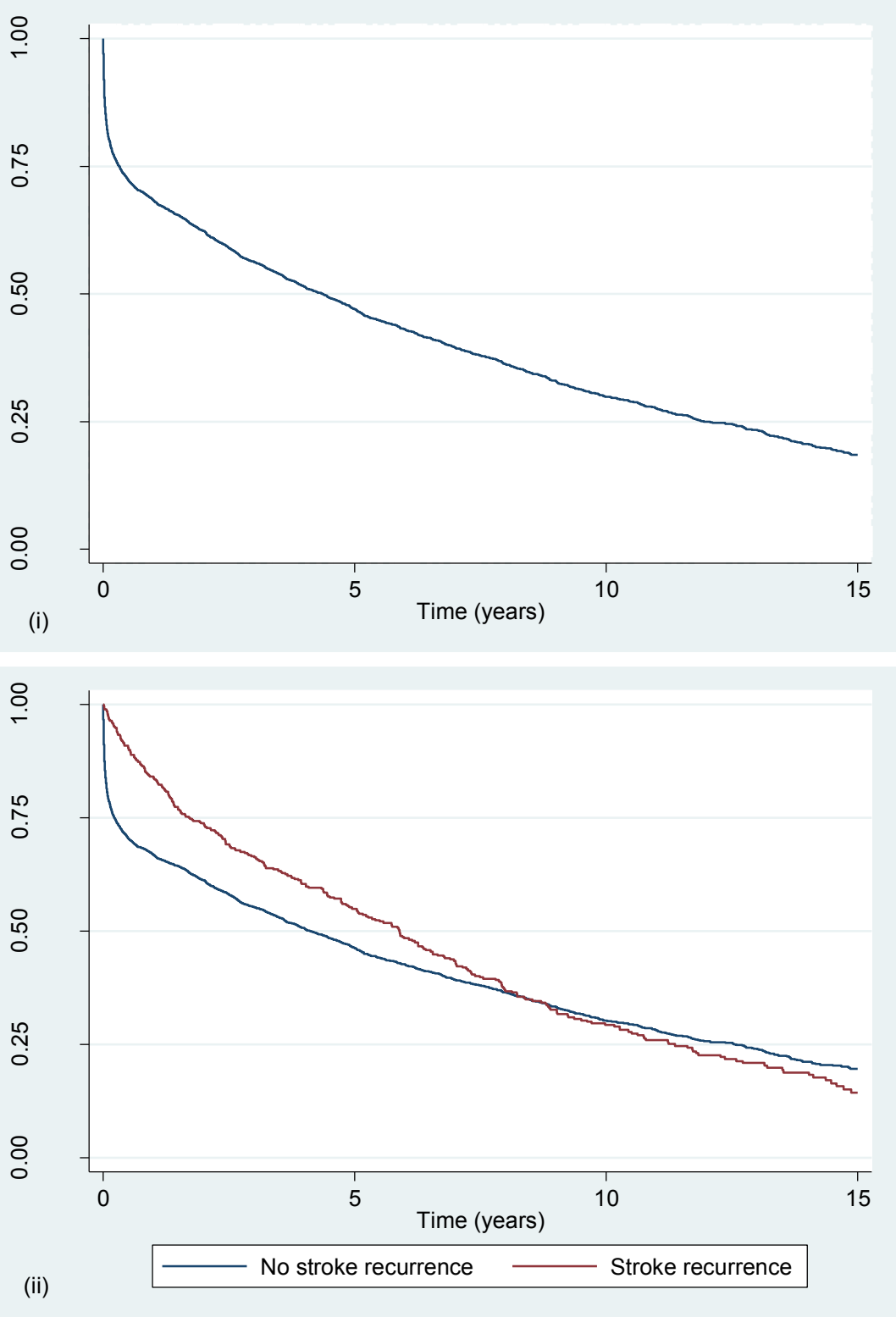

Figure 15. i) Survival probability (1- risk of death) up to 15 years after first stroke; ii) Survival up to 15 years stratified by stroke recurrence

7.3.2.2 Multivariable analyses

The multivariable analyses estimating the effect of stroke recurrence on the risk of death when adjusted for the socio-demographic, case-mix, prior to stroke risk factors, process of care and time-dependent variables, up to 1, 5, 10 and 15 years after first stroke are shown in Table 32. It is notable that in these analyses stroke recurrence is estimated as a binary (no recurrence/recurrence) variable. Stratified Cox proportional hazards models were fit for each time-point analysed, and the proportional hazards assumption was found to be fulfilled across all variables included in the model.

After adjustment for the risk factors mentioned above, stroke recurrence was found to significantly increase the risk of death at all time points analysed and was therefore a predictor. In particular, stroke recurrence conferred over six times the risk of death up to 1 year after first stroke, compared to those without a stroke recurrence HR 6.30(95% 4.60-8.62). However, even up to 15 years after first stroke, second stroke was associated with twice the risk of death compared to those without a recurrence HR 2.18(95% 1.88-2.52).

Further multivariable analyses estimating the effect of stroke recurrence on risk of death were carried out. Analyses were once more adjusted for the variables described above, but stroke recurrence was categorised according to when the recurrence took place i.e. up to 3 months, 1 year, 5 years, and 10 years after first stroke to identify if this is an important factor. The results of these analyses are displayed in Table 33, Table 34, Table 35 and Table 36.

These multivariable results demonstrate that a stroke recurrence occurring at all time-points up to 10 years after first stroke, was associated with an increased risk of death. This increased risk was found to be evident at all time-points analysed, up to 15 years after first stroke. Stroke recurrence within the first year after initial stroke was particularly associated with increased risk of death at all time points. Of note, the risk of death up to 1 year after stroke was over five times higher in those with a stroke

recurrence by 3 months (HR 5.45(95%CI 3.46-8.59%), and eight time higher in those with a stroke recurrence by 1 year (HR 8.08(95%CI 5.27-12.4%) compared to those without a stroke recurrence.

The results displayed in Tables 33 to 36 demonstrate that regardless of how early or late the stroke recurrence occurs, individuals remain at approximately double the risk of death even up to 15 years after the first stroke. Whilst remaining a significant predictor for increased risk of death throughout the study period, the results reported up to 10 and 15 years after first stroke, show a slightly decreased hazard ratio if a stroke recurrence occurred before 5 years after first stroke compared to the other time-points analysed. For both time-points, hazard ratios of approximately 1.8, with 95% Confidence Intervals of approximately 1.4-2.3 were obtained, compared to hazards of 2.4 (95%CI approximately 1.8-3.4%) estimated if the stroke recurrence occurred up to 3 months, 1 year, and 10 years after first stroke.

None of the interactions tested were found to be significant and therefore the results have not been presented stratified.

	1 Year		5 Years		10 Years		15 Years	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Stroke recurrence								
No	1	<0.001	1	<0.001	1	<0.001	1	<0.001
Yes	6.30(4.60-8.62)		2.63(2.18-3.18)		2.25(1.93-2.62)		2.18(1.88-2.52)	
Age group								
>65	1	<0.001	1	<0.001	1	<0.001	1	<0.001
65-74	2.49(1.89-3.29)		2.49(2.05-3.02)		2.48(2.11-2.92)		2.50(2.14-2.91)	
>75	3.54(2.71-4.63)		4.42(3.68-5.32)		4.52(3.86-5.29)		4.46(3.84-5.17)	
Gender								
Male	1	0.508	1	0.392	1	0.482	1	0.274
Female	0.95(0.82-1.10)		0.95(0.86-1.06)		0.97(0.88-1.06)		0.95(0.87-1.04)	
Ethnicity								
White	1	<0.001	1	<0.001	1	<0.001	1	<0.001
Black	0.67(0.54-0.82)		0.70(0.60-0.82)		0.68(0.59-0.77)		0.68(0.60-0.77)	
Other	0.63(0.43-0.92)		0.68(0.51-0.88)		0.64(0.50-0.80)		0.66(0.53-0.82)	
Socio economic status								
Non-manual	1	<0.001	1	<0.001	1	<0.001	1	<0.001
Manual	1.20(1.00-1.44)		1.19(1.05-1.36)		1.11(1.00-1.24)		1.11(1.00-1.24)	
Unknown	3.10(2.10-4.58)		2.46(1.78-3.40)		1.88(1.40-2.55)		1.79(1.34-2.40)	
Economically inactive	1.89(1.52-2.34)		1.76(1.48-2.09)		1.68(1.44-1.96)		1.69(1.45-1.97)	
Stroke Subtype								
Infarct	1	0.079	1	0.629	1	0.206	1	0.251
PICH	1.21(1.00-1.47)		0.93(0.79-1.09)		0.95(0.82-1.09)		0.94(0.82-1.09)	
SAH	1.32(0.93-1.87)		0.94(0.69-1.30)		0.78(0.58-1.05)		0.81(0.61-1.07)	
Year of initial stroke								
1995-1998	1	<0.001	1	<0.001	1	<0.001	1	<0.001
1999-2002	0.69(0.58-0.82)		0.71(0.62-0.82)		0.73(0.64-0.82)		0.74(0.66-0.84)	
2003-2006	0.42(0.32-0.55)		0.57(0.48-0.68)		0.60(0.51-0.70)		0.60(0.51-0.70)	
2007-2011	0.66(0.52-0.83)		0.76(0.63-0.91)		0.74(0.62-0.88)		0.73(0.62-0.87)	
Risk factors								
No hypertension	1	0.195	1	0.301	1	0.406	1	0.804
Hypertension	0.91(0.78-1.05)		0.94(0.84-1.06)		0.96(0.86-1.06)		0.99(0.891.09)	
No anti-hypertensives	1	<0.001	1	<0.001	1	<0.001	1	<0.001
Anti-hypertensives at 3m	0.91(0.67-1.24)		0.97(0.82-1.13)		1.06(0.93-1.21)		1.05(0.92-1.19)	
Unknown	8.44(6.67-10.68)		3.22(2.79-3.72)		2.59(2.28-2.95)		2.52(2.23-2.85)	
Stroke severity								
GCS <13	1	<0.001	1	<0.001	1	<0.001	1	<0.001
13-15	0.30(0.26-0.35)		0.38(0.34-0.43)		0.42(0.39-0.47)		0.43(0.38-0.47)	
Process of care								
Not admitted to hospital	1	<0.001	1	<0.001	1	<0.001	1	<0.001
Admitted to general medical ward	3.68(2.47-5.49)		2.44(1.97-3.07)		2.12(1.78-2.53)		1.92(1.63-2.26)	
Admitted to Stroke Unit	2.71(1.81-4.07)		1.90(1.52-2.39)		1.82(1.52-2.19)		1.71(1.44-2.04)	
Unknown	3.42(1.71-6.84)		1.91(1.08-3.39)		1.79(1.04-3.07)		1.67(0.98-2.86)	

Table 32 Multivariable analyses using stratified Cox Proportional Hazards models 1: the cumulative risk of death up to 1, 5, 10 and 15 years post-first stroke*

*Analyses restricted to patients without missing values

	HR (95%CI)	P value
Stroke recurrence		
No	1	<0.001
<3m	5.45(3.46-8.59)	
1 year	8.08(5.27-12.4)	
Age group		
<65	1	<0.001
65-74	2.48(1.88-3.26)	
>75	3.55(2.71-4.64)	
Gender		
Male	1	0.511
Female	0.95(0.82-1.10)	
Ethnicity		
White	1	<0.001
Black	0.67(0.55-0.83)	
Other	0.63(0.43-0.92)	
Socio economic status		
Non-manual	1	<0.001
Manual	1.19(0.99-1.43)	
Unknown	3.02(2.05-4.47)	
Economically inactive	1.87(1.51-2.32)	
Stroke Subtype		
Infarct	1	0.079
PICH	1.21(0.99-1.47)	
SAH	1.33(0.94-1.89)	
Year of initial stroke		
1995-1998	1	<0.001
1999-2002	0.68(0.57-0.81)	
2003-2006	0.42(0.32-0.55)	
2007-2011	0.65(0.52-0.82)	
Risk factors		
No hypertension	1	0.173
Hypertension	0.90(0.78-1.05)	
No anti-hypertensive medication	1	<0.001
Anti-hypertensive medication at 3m	0.93(0.68-1.26)	
Unknown anti-hypertensive medication	8.49(6.71-10.75)	
Stroke severity		
GCS <13	1	<0.001
13-15	0.30(0.26-0.35)	
Process of care		
Not admitted to hospital	1	<0.001
Admitted to general medical ward	3.70(2.48-5.52)	
Admitted to Stroke Unit	2.72(1.81-4.08)	
Unknown	3.43(1.71-6.86)	

Table 33 Multivariable analyses 2: the cumulative risk of death up to 1 year post-initial stroke *

*Analyses restricted to patients without missing values

	HR (95%CI)	P value
Stroke recurrence		
No	1	<0.001
<3m	2.79 (1.95-4.00)	
1 year	2.82 (2.14-3.72)	
5 years	2.31 (1.66-3.20)	
Age group		
<65	1	<0.001
65-74	2.49(2.05-3.02)	
>75	4.45(3.70-5.35)	
Gender		
Male	1	0.361
Female	0.95(0.85-1.06)	
Ethnicity		
White	1	<0.001
Black	0.70(0.61-0.82)	
Other	0.66(0.50-0.87)	
Socio economic status		
Non-manual	1	<0.001
Manual	1.19(1.05-1.35)	
Unknown	2.44(1.76-3.37)	
Economically inactive	1.76(1.48-2.08)	
Stroke Subtype		
Infarct	1	0.627
PICH	0.93(0.79-1.09)	
SAH	0.94(0.68-1.29)	
Year of initial stroke		
1995-1998	1	<0.001
1999-2002	0.71(0.62-0.82)	
2003-2006	0.57(0.48-0.68)	
2007-2011	0.75(0.63-0.90)	
Risk factors		
No hypertension	1	0.295
Hypertension	0.94(0.84-1.06)	
No anti-hypertensive medication	1	<0.001
Anti-hypertensive medication at 3m	0.97(0.82-1.13)	
Unknown anti-hypertensive medication	3.22(2.79-3.72)	
Stroke severity		
GCS <13	1	<0.001
13-15	0.38(0.34-0.43)	
Process of care		
Not admitted to hospital	1	<0.001
Admitted to general medical ward	2.42(1.95-3.01)	
Admitted to Stroke Unit	1.88(1.50-2.36)	
Unknown	1.89(1.07-3.36)	

Table 34 Multivariable analyses 3: the cumulative risk of death up to 5 years post-initial stroke *

*Analyses restricted to patients without missing values

	HR (95%CI)	P value
Stroke recurrence		
No	1	<0.001
<3m	2.46(1.77-3.40)	
1 year	2.44(1.92-3.11)	
5 years	1.85(1.44-2.38)	
10 years	3.08(2.00-4.73)	
Age group		
<65	1	<0.001
65-74	2.49(2.12-2.93)	
>75	4.54(3.88-5.32)	
Gender		
Male	1	0.405
Female	0.96(0.87-1.06)	
Ethnicity		
White	1	<0.001
Black	0.68(0.60-0.78)	
Other	0.63(0.50-0.80)	
Socio economic status		
Non-manual	1	<0.001
Manual	1.11(0.99-1.24)	
Unknown	1.87(1.38-2.53)	
Economically inactive	1.69(1.44-1.98)	
Stroke Subtype		
Infarct	1	0.202
PICH	0.95(0.82-1.10)	
SAH	0.78(0.58-1.05)	
Year of initial stroke		
1995-1998	1	<0.001
1999-2002	0.73(0.64-0.82)	
2003-2006	0.60(0.51-0.70)	
2007-2011	0.74(0.62-0.88)	
Risk factors		
No hypertension	1	0.418
Hypertension	0.96(0.86-1.06)	
No anti-hypertensive medication	1	<0.001
Anti-hypertensive medication at 3m	1.06(0.92-1.21)	
Unknown anti-hypertensive medication	2.58(2.27-3.03)	
Stroke severity		
GCS <13	1	<0.001
13-15	0.42(0.38-0.47)	
Process of care		
Not admitted to hospital	1	<0.001
Admitted to general medical ward	2.08(1.75-2.49)	
Admitted to Stroke Unit	1.80(1.49-2.16)	
Unknown	1.76(1.03-3.03)	

Table 35 Multivariable analyses 4: the cumulative risk of death up to 10 years post-initial stroke *

*Analyses restricted to patients without missing values

	HR (95%CI)	P value
Stroke recurrence		
No	1	<0.001
<3m	2.46(1.79-3.38)	
1 year	2.41(1.91-3.04)	
5 years	1.81(1.43-2.29)	
10 years	2.41 (1.68-3.47)	
Age group		
<65	1	<0.001
65-74	2.51(2.16-2.93)	
>75	4.49(3.87-5.21)	
Gender		
Male	1	0.224
Female	0.94(0.86-1.04)	
Ethnicity		
White	1	<0.001
Black	0.68(0.60-0.77)	
Other	0.65(0.52-0.82)	
Socio economic status		
Non-manual	1	<0.001
Manual	1.10(0.99-1.23)	
Unknown	1.77(1.32-2.37)	
Economically inactive	1.70(1.45-1.98)	
Stroke Subtype		
Infarct	1	0.247
PICH	0.95(0.82-1.09)	
SAH	0.80(0.61-1.06)	
Year of initial stroke		
1995-1998	1	<0.001
1999-2002	0.74(0.66-0.83)	
2003-2006	0.59(0.51-0.69)	
2007-2011	0.73(0.61-0.87)	
Risk factors		
No hypertension	1	0.799
Hypertension	0.99(0.90-1.09)	
No anti-hypertensive medication	1	<0.001
Anti-hypertensive medication at 3m	1.06(0.93-1.20)	
Unknown anti-hypertensive medication	2.61(2.31-2.97)	
Stroke severity		
GCS <13	1	<0.001
13-15	0.4530.38-0.47)	
Process of care		
Not admitted to hospital	1	<0.001
Admitted to general medical ward	1.89(1.60-2.22)	
Admitted to Stroke Unit	1.69(1.42-2.00)	
Unknown	1.65(0.96-2.82)	

Table 36 Multivariable analyses 5: the cumulative risk of death up to 15 years post-initial stroke *

*Analyses restricted to patients without missing values

7.4 Discussion

This chapter investigates the association between stroke recurrence and the risk of death up to 15 years after first stroke. The results demonstrate that stroke recurrence increases the risk of death after initial stroke, and this increased risk is maintained up to 15 years after the first stroke. Stroke recurrence at any time during the follow-up period is associated with a significantly higher risk of death, however within the first year recurrence was shown to be particularly important with the very high risk of death conferred persisting up until the end of the 15 year study period.

Of note, the risk of death 1 year after first stroke was over five times higher in those with a stroke recurrence by 3 months (HR 5.45(95%CI 3.46-8.59%), and eight time higher in those with a recurrence by 1 year (HR 8.08(95%CI 5.27-12.4%) compared to those without a stroke recurrence. The results demonstrate poor prognosis in those with early stroke recurrence, emphasising the need for effective and timely stroke management at the time of first stroke, in order to prevent second strokes occurring.

The UK National Clinical Guidelines for Stroke, published by the Royal College of Physicians in 2012, recommends that appropriate secondary prevention be instigated as soon as possible after first stroke, usually in the acute phase if safe to do so. However, the number of trials supporting this hypothesis are fewer than those for primary prevention and many of the studies cited as evidence, report outcomes after TIA rather than stroke only[43, 44]. As mentioned in Chapter 6, secondary prevention medications have been shown not just to reduce the risk of recurrence, but to have a role in reducing the overall cardiovascular disease burden by lowering mortality and morbidity rates[46]. Kong *et al* conducted a hospital based study in China looking at the predictors of 1 year death and disability in women after ischaemic stroke. They found suboptimal use of antiplatelet agents and anti-hypertensive therapies to be independent predictors of increased risk of death 1 year after first stroke[194].

Antiplatelet agents were also identified by Ding *et al* as independent protective predictors of all-cause death (hazard ratio (HR) 0.42; 95% confidence interval (CI) 0.21-0.86; P=0.017) and recurrent cerebrovascular events (HR 0.58; 95%CI 0.36-0.92; P=0.021). Their study, a multi-centre hospital-based study of patients after ischaemic stroke, was again undertaken in China and further studies are needed to ascertain if these results are generalisable to other non-Chinese populations.

There may also be differences in risk of stroke recurrence between stroke subtypes. Previous studies from the SLSR found no differences in the risk of recurrence between ischaemic and haemorrhagic strokes up to 10 years after first stroke[133]. Even among ischaemic stroke subtypes, differences in risk of stroke recurrence at different time points have been found. As mentioned in Chapter 5, Lovett *et al*, studying the risk of recurrent stroke by aetiological TOAST subtype, found patients with the LAA subtype were consistently three times more likely to have a stroke recurrence up to 3 months after first stroke, compared to other aetiological subtypes[161]. However studies have also demonstrated an increased risk of death amongst patients with an initial LAA subtype stroke compared to other ischaemic stroke subtypes without a stroke recurrence, up to 5 years after first stroke[183] indicating that this group may be increasingly disadvantaged and be at considerable risk of poorer outcomes if risk factors are not identified and managed adequately at the time of initial stroke.

The analyses in this chapter also suggest an increased risk of death in those with a stroke recurrence up to both 5 and 10 years after first stroke when compared to those with no recurrence. It is notable that whilst the risk of death has been estimated to increase at all time-points, the effect of a stroke recurrence up to 5 years after first stroke is decreased compared to the hazard estimated for a stroke recurrence up to 10 years.

These results may be again be indicative of the subtype of the initial stroke. Studies from the SLSR have previously suggested that hypertension gains importance as a

predictor for stroke recurrence 5 and 10 years after first stroke[133]. Hypertension is associated with small vessel disease which is pathognomonic of the small vessel occlusion (SVO) subtype, and has been shown to be the aetiological cause of lacunar infarcts, generally considered to be related to less severe strokes. Therefore, patients with small vessel disease may experience a less severe stroke recurrence later than other stroke subtypes and may have better than expected survival after recurrence as a result of tight blood pressure control[124]. As described in Chapter 5, studies have shown the SVO stroke subtype to have increased odds of an excellent outcome, defined as a combination of a Glasgow Outcome Scale score of 1 and a Barthels Index score of 19 or 20 (on a scale of 0 to 20), at 3 months[20]; to have the highest rates of independent patients, as defined by Rankin scale scores of 1-2, at 6 months[164]; and to have an increased risk of survival 1 and 2 years after first stroke compared to other TOAST subtypes[1, 108, 165].

Finally, it is important to note that death is not the only outcome of relevance post-stroke. It would be useful to repeat these analyses to include the effect of stroke recurrence on risk of disability measured by the Barthels Index, or using a composite measure to combine the risk of disability and death after a recurrent stroke. Again these analyses could be conducted as future analyses related to this thesis.

Multivariable analyses were used to reduce the risk of confounding in this study as analyses were adjusted for variables thought to be impact the risk of death after first stroke. In particular, the adjustment of the statistical model to take into account the association between risk of death and stroke recurrence is a strength of these analyses and has not been demonstrated previously in similar analyses published in the literature.

However, even with the substantial adjustments undertaken it is probable that a degree of residual confounding remained in the analyses. In particular, other cardiovascular risk factors may be important predictors of increased risk of death. These important factors, such as a previous history of atrial fibrillation or previous

myocardial infarction have been shown in other studies to be important predictors of death, but only for ischaemic strokes[195, 196]. Due to the total number of stroke recurrences being only approximately 400, the study results were not stratified for stroke subtype, and therefore these cardiovascular risk factors were not adjusted for in the analyses. For similar reasons, the role of secondary prevention in reducing the risk of death after first stroke was not explored further as antiplatelet and anti-cholesterol medications, both adjusted for in the analyses in Chapter 6, are commonly used as secondary prevention after ischaemic stroke[29].

Another advantage is the ability for these results to be generalised to other populations, again due to the robust methods used in the analyses. Despite the methodological differences between stroke studies discussed in Chapter 4 of this thesis, and the ethnic diversity, considered to be a key strength of the SLSR population with only 56% self-defining themselves as being of a White ethnicity compared to 86% of the UK population[79], it could be possible to estimate the effect of stroke recurrence on risk of death after first stroke across the whole UK using national stroke data and data from the General Practice Research Database (GPRD)[197]. This requires data related to stroke recurrence and the other explanatory variables adjusted for in these analyses to be consistently collected. However, at the current time, these data are not collected across the UK.

The impact of missing data on the results may also be important. In this study the highest percentage of data missing from the baseline variables analysed was 7.3% of data missing from the GCS stroke severity variable. As this is generally considered to be a low level of missingness, sensitivity analyses were not performed due to time constraints. However, it is important for sensitivity analyses to be considered as a part of future analyses, in order to better understand the impact of the missing data on the risk of death estimated in this study.

Since 1999 ethnic differences in survival after stroke have been described within the SLSR population, with the black population demonstrating a clear survival advantage

over the white population [13]. Therefore possible interactions between ethnicity and the other explanatory variables were tested. As none of the interactions tested were found to be significant the results were not stratified, but it is important to acknowledge that other variables, for example age or sex, could potentially also cause interactions. Further analyses could be conducted to identify other significant interactions within these analyses.

7.5 Summary

This chapter demonstrates that increased risk of death in individuals with a recurrence at all time-points after initial stroke, is maintained up to 15 years after first stroke. The analyses highlight the first year after stroke as a particularly critical time-period during which patients should be followed up regularly in order for risk factors to be aggressively managed.

An important challenge remaining for both Stroke Physicians and policy researchers is how to accurately identify those at increased risk of early stroke recurrence. However this is achieved, this study highlights that early identification and risk factor modification is paramount, both to reduce the risk of stroke recurrence, but to also to reduce the risk and impact of premature death in both the early and long-term period after initial stroke.

Chapter 8 Conclusions

8.1 Summary of findings

This thesis was designed to estimate the natural history of stroke recurrence after first-ever stroke, using the population-based South London Stroke Register as a sampling frame.

The systematic review and meta-analysis presented in Chapter 4 of this thesis identified 16 studies published between 1994 and 2009 estimating the cumulative risk of stroke recurrence at time points from 30 days to 10 years after first stroke, of which, 13 studies contained sufficient data to be included in the meta-analysis. The pooled cumulative risk of stroke recurrence was 3.1% (95% CI 1.7-4.4) by 30 days; 11.1% (95% CI 9.0-13.3) by 1 year; 26.4% (95% CI 20.1-32.8) by 5 years; and 39.2% (95% CI 27.2-51.2) by 10 years after initial stroke. A temporal reduction in the risk of stroke recurrence was found across the different study populations, with smaller recurrence risk reported in later studies. Substantial heterogeneity was found between the studies at all time points with I^2 values ranging from 88-96%.

Whilst there were undoubtedly methodological differences between the study populations such as differences in case inclusion, and differences in definition of both a stroke an differences between populations and temporal changes in stroke management and secondary prevention may also be important in explaining these results.

Meta-regression models were fit to the cumulative risk of stroke recurrence of the individual studies and pooled estimates of the cumulative risk of stroke recurrence were calculated with 95% Confidence Intervals. The Exponential model fit was shown to under-estimate the risk of stroke recurrence up to approximately 6 years after first stroke, after which time the model over-estimated the predicted risk. A

Weibull model was then fit to the results, which closely followed the pooled estimates up to 10 years after first stroke.

The South London Stroke Register, a prospective longitudinal population-based stroke register, established in a multi-ethnic, inner city population of 271,817, meets the criteria to be an ideal sampling frame to estimate the natural history of stroke recurrence up to 12 years after first-ever stroke. Predictors for stroke recurrence were identified from variables including socio-demographic factors, risk factors diagnosed at the time of initial stroke, patterns in stroke subtype, and stroke severity markers, taking into account the effect of temporal changes in stroke management, e.g. the use of secondary prevention medication.

The results of the analyses of the SLSR data presented in this thesis showed the cumulative risk of first stroke recurrence up to 1 year, 5 years and 10 years to be 7.1% (95% CI 6.0 to 8.3%), 16.2% (95% CI 14.4 to 18.1%) and 24.5% (95% CI 21.3 to 27.9%) respectively. At all time-points from 1 year up to 10 years after first stroke, the presence of cardiovascular risk factors at time of first stroke were shown to increase the risk of stroke recurrence. However time trend analyses suggest a reduction in risk of stroke recurrence 1 year after first stroke between 1995-1999, 2000-2004, and 2005-2009 (p=0.03).

When differences between aetiological stroke subtypes were analysed for strokes registered with the SLSR between 1999 and 2009 only, the cumulative risk of stroke recurrence up to 1 year after first stroke ranged from 4.0% in the small vessel occlusion (SVO) group to 6.5% in the large artery occlusion (LAA) group. These results were lower than 1 year recurrence rates for both intracerebral (PICH) and sub-arachnoid (SAH) haemorrhages which were 8.6% and 8.8% respectively. Transition in aetiological subtype between initial and recurrent stroke was seen in 51.0% at 1 year, increasing to 61.9% 10 years after first stroke.

The use of time-dependent Cox proportional hazard models estimating the association between time-dependent risk factor modification on the risk of stroke

recurrence up to 5 years after first stroke demonstrated a general decrease in hazard ratios estimating risk of stroke recurrence when patients were on anti-hypertensive and anticoagulant medications compared those untreated. However only the use of lipid-lowering medications in those with a diagnosis of hypercholesterolaemia demonstrated a reduction in stroke recurrence risk. By 12 years a general decrease in hazard ratios were also reported however the use of statins and other agents to reduce hypercholesterolaemia showed statistical significance for both all strokes and for ischaemic strokes only. The analyses demonstrated no significant associations in this cohort between stroke recurrence and prescription of other effective secondary prevention, but the analyses cannot exclude a Type 2 error.

The risk of death 1, 5, 10 and 15 years after initial stroke was 31.7% (95% CI 30.3 to 33.1%), 52.9% (95% CI 51.4 to 54.5%), 70.2% (95% CI 68.5 to 71.8%) and 81.6% (95%CI 79.6 to 83.5%) respectively. The association of stroke recurrence on risk of death after first stroke was estimated and stroke recurrence was found to significantly increase the risk of death at all time points analysed. When stroke recurrence was categorised according to when the recurrence took place, increased risk was found at all time-points up to 15 years after first stroke. Stroke recurrence within the first year after initial stroke was particularly associated with increased risk of death at all time points.

8.2 Strengths and limitations of this thesis

The main strengths of this thesis are related to the methods used. This thesis presents estimates of cumulative risk and predictors of stroke recurrence up to 12 years after first stroke using a well-established population-based sampling frame which meets recognised criteria to allow comparability of stroke incidence[75]. The overlapping notification sources and capture-recapture techniques used at the SLSR provide methodological robustness due to high levels of completeness of the stroke ascertainment.

The thesis uses meta-regression to develop predictive models to best estimate the risk of stroke recurrence at time-points not analysed directly. The analyses conducted using both pooled estimates from the meta-analyses and the SLSR dataset, demonstrate the risk of stroke recurrence follows a Weibull distribution, therefore challenging the assumptions made in previous literature, that the distribution was unknown.

The use of time-dependent survival analyses to estimate the association between secondary prevention variables and risk of stroke recurrence, and to adjust for associations between death and stroke recurrence is another strength of this thesis. In particular, adjusting the results to account for an individual dying from a non-stroke related cause and therefore not being alive for a recurrence to occur, reduces the risk of under-estimation of the association between stroke recurrence and risk of death.

The main limitations of this thesis are also methodological. In order to obtain the longitudinal estimates recorded in the study, long-term data collection is needed. The limitations of this long-term dataset, such as missing data, were addressed by recollecting stroke recurrence data to reduce missingness; by the derivation and application of an algorithm to ONS death data to increase completeness of case ascertainment; and by statistical methods including sensitivity analyses. Whilst the degree of missingness in variables used in the analyses is generally low, certain risk factors or stroke subtype classifications e.g. the TOAST classification, have only been cited as important in recent years, and so have not been collected at the SLSR since 1995, leading to incomplete variables within the SLSR dataset. Missing data also plays a role during the follow-up of individuals at risk of stroke recurrence. Whilst multiple imputation methods used to create an imputed dataset for sensitivity analyses in Chapter 3 of this thesis, produced similar predictors of stroke recurrence compared to the dataset used in the main analyses, the impact of missing data during patient follow-up on risk of stroke recurrence remains unclear. Whilst this missing data has been presumed to be missing at random i.e. not related to an

individual having a stroke recurrence, further work is needed to confirm this assumption.

The other main limitation of this thesis relates to sample size. Just under 400 stroke recurrences were recorded at the SLSR during the study period. .As discussed in Chapter 6, whilst the stroke recurrence to predictor variable ratio was greater than 10 for most of the analyses undertaken in this thesis, studies by Peduzzi et al indicate that under-estimation of the event hazard are more likely to occur at lower recurrence to predictor ratios[176]. Pooling data from different stroke registers could provide a larger sampling frame for future pooled or individual level meta-analyses to be developed.

8.3 My personal development whilst undertaking this thesis

This thesis was a steep learning curve for me. I began the research for this thesis, having been working as a hospital medical registrar, and with no previous statistics training or experience of using statistical software packages. I learned how to apply the necessary statistical and epidemiological methods to answer the questions posed in this thesis, however this did pose problems when analyses terminated unexpectedly, or did not run as expected, and often I had to learn more in order to work out what I had done wrong. This made undertaking the statistical analyses presented in this thesis a long process.

However this also meant that I was presented with many opportunities to develop and learn new skills, in particular related to statistical methods, whilst undertaking this thesis. I learned to use three difference statistical packages (SPSS, STATA and SAS) in order to undertake the analyses presented.

I feel that I made good use of the opportunities presented to me during this thesis, however ideally if I had my time again I would ensure I completed my thesis prior to

leaving the South London Stroke Register in 2011. Combining full-time Public Health speciality training with writing this thesis made it more difficult to maintain momentum and contributed to this thesis being submitted just prior to the six year submission deadline.

There were many reasons why this thesis was not completed sooner. One reason was that the time allocated for the re-collection of the stroke recurrence data, which I undertook between 2009-2011 in order to improve data quality, proved to be insufficient. The data collection relied heavily on microfiche records being transported back to London from data storage facilities and then being reviewed page by page in order to obtain the necessary information. In total this data collection exercise took almost two years.

During my four years working on the SLSR, I learned first-hand about the challenges of working on a longitudinal epidemiological study, whilst learning about the clinical and radiological features related to a diagnosis of stroke and stroke recurrence from expert stroke physicians. I also had the opportunity to present my research at international and national conferences, to write articles for publication in peer-reviewed journals, and to contribute to book chapters.

8.4 Implications of results for public health and clinical practice

This thesis has produced important results with implications for stroke service planning and resource allocation. The annual costs of stroke in the UK are estimated to be between £3.7 billion and £8 billion, including direct health care costs, productivity loses due to mortality and morbidity, and informal care costs[11, 198]. In 2010, Round 7 of The Royal College of Physicians (RCP) National Sentinel Stroke Clinical Audit found that 81% of patients admitted to hospital with stroke had known vascular risk factors, 29% had a previous stroke or TIA and 57% had a previous diagnosis of hypertension[199]. Yet the RCP report commented that:

'*The evidence from this audit is that there is still more that could be done at a critical time of a patient's life to modify lifestyle stroke risk factors with only just over half of patients having documented evidence of such risk factors being discussed'*[199].

The *'Progress in improving stroke care'* survey conducted by the National Audit Office in 2010 similarly indicated that there is more work to be done regarding risk factor management after first stroke[200]. This online and postal survey, conducted between June to September 2009, gathered the views of 760 people with stroke or who cared for people with stroke. Only half of respondents said they received advice on further stroke prevention when leaving hospital, with a third of patients not receiving a follow-up appointment within six weeks of their first stroke.

As mentioned earlier in this thesis, The UK National Clinical Guidelines for Stroke, published by the Royal College of Physicians in 2012, recommends that appropriate secondary prevention be instigated as soon as possible after first stroke, usually in the acute phase if safe to do so. However, the number of trials supporting this hypothesis are fewer than those for primary prevention and many of the studies cited as evidence, report outcomes after TIA rather than stroke only[43].

The analyses in this thesis provide long-term estimates about the cumulative risk of stroke recurrence. The results highlight the importance of stroke aetiology in predicting increase risk of both stroke recurrence and death after first stroke, and suggest that the critical period for stroke recurrence may vary according to the aetiological subtype of the first stroke. However the results identify the first year after a stroke as a critical time-period during which significantly increased risk of death conveyed on an individual having a stroke recurrence is maintained for at least the next 15 years. This provides evidence that intensive risk factor management and lifestyle modification during the first year after stroke is important both for individuals and to reduce the future impact on healthcare services, although stroke recurrence

throughout the decade after first stroke was shown to significantly increase the risk of death compared to no recurrence.

Individuals at high-risk of stroke recurrence should therefore be quickly identified by clinicians at the time of first stroke and secondary prevention medication initiated. They should receive regular primary care follow-up to ensure these risk factors are aggressively monitored to reduce the risk of stroke recurrence.

Risk factor management after stroke features as part of the Quality and Outcomes Framework (QOF), the voluntary annual reward and incentive programme for all GP surgeries. Updated QOF Indicators are produced annually by the National Institute for Health and Care Excellence (NICE) and used by the four UK nations to set QOF indicators for the coming year[201]. The QOF contains five main components,: Clinical; Public Health; Public Health - Additional Services; Patient Experience; Quality and Productivity. Each domain consists of a set of achievement measures, known as indicators, against which each practice score points according to their level of achievement.

The QOF 2015-16 includes 5 indicators specifically related to patients with stroke and TIA, with no changes recommended compared to last year[202]. These indicators are displayed in Table 37. It is notable that the stroke-specific QOF indicators relate primarily to the identification and management of risk factors after first stroke or TIA and therefore support the conclusions drawn from this thesis that regular primary care follow-up is needed to ensure risk factors are aggressively monitored to reduce the risk of stroke recurrence. However it is important that the QOF indicators are not considered to be the extent of risk-factor management after stroke or TIA but that patients at high-risk of stroke recurrence have access to more regular review by primary care professionals, if necessary, in order to establish and maintain optimum cardiovascular risk factor control.

QOF 2015-16 indicator	Threshold required
The contractor establishes and maintains a register of patients with stroke or TIA	-
The percentage of patients with a stroke or TIA (diagnosed on or after 1 April 2014) who have a record of a referral for further investigation between 3 months before or 1 month after the date of the latest recorded stroke or the first TIA	45-80%
The percentage of patients with a history of stroke or TIA in whom the last blood pressure reading (measured in the preceding 12 months) is 150/90 mmHg or less	40-75%
The percentage of patients with stroke or TIA who have had influenza immunisation in the preceding 1 August to 31 March	55-95%
The percentage of patients with a stroke shown to be non- haemorrhagic, or a history of TIA, who have a record in the preceding 12 months that an anti-platelet agent, or an anti- coagulant is being taken	57-97%

Table 37. The QOF 2015-16 indicators related to stroke and TIA

Accurate identification of individuals at high risk of a stroke recurrence can pose a significant challenge, and further work is needed to develop and trial stroke-specific prognostic indicators with a high sensitivity and specificity for identifying those at high-risk of early stroke recurrence. By preventing early stroke recurrences, significant and long-lasting reductions in risk of death after stroke can be made, regardless of initial stroke subtype, severity, or the age of the patient.

Poor adherence to secondary prevention is undoubtedly an important factor in risk factor management and needs to be addressed. Younger age, incomplete understanding of perceived benefit of medication, poor cognitive function and a lack of routine have been identified as key reasons for non-compliance amongst stroke patients[169]. However, work needs to be undertaken to optimise secondary prevention plans for all stroke patients, with a particular emphasis on older patients and those without co-existing coronary heart disease, who been found to be associated with lower rates of prescribed secondary prevention medication[203].

8.5 Implications for future research

This thesis explores the natural history of stroke recurrence using the population-based South London Stroke Register as a sampling frame. The results present a broad basis for future research related to a variety of different themes presented in this thesis. A key area for future study involves further investigation of the association between the prescription of secondary prevention and the risk of stroke recurrence. There are many ways this work could be built on, for example, by re-categorising the time-dependent variables to amalgamate the 'unknown' categories. It would also be important to minimise missing data, and an alternative could be for current risk factor levels to be ascertained, by incorporating recent blood pressure readings and blood test results, for example using a patient's most recent low-density-lipoprotein (LDL) cholesterol levels as a marker of current hypercholesterolaemia status at the time of follow-up interview.

Further research should also be undertaken looking at the effect of time on stroke recurrence in particular by identifying time-trends in the use and association of secondary prevention and risk of stroke recurrence. This could be achieved by including a year of initial stroke covariate into multivariable analyses to allow adjustment.

It was demonstrated in Chapter 4 of this thesis that despite methodological differences between different study populations, useful conclusions can be drawn by using a larger sampling frame, for example a meta-analysis of stroke registers to study the association between secondary prevention and risk of stroke recurrence. As mentioned in Chapter 4, it is important to differentiate studies using stroke only as the first 'event' from studies using stroke and transient ischaemic attack as a composite start point for analyses in order for results from different stroke registers to be accurately compared.

As described in Chapter 7, death is not the only outcome of relevance in the post-stroke period and the effect of stroke recurrence on other outcomes, such as disability, dementia or depression would provide a important information to build a more complete picture of the natural history of stroke recurrence. The results described in this thesis and could be used in the development of a predictive tool to help clinicians estimate the risk of stroke recurrence for an individual patient based on key predictors identified at the time of initial stroke, and in the post-stroke period. As outlined in Chapter 1 of this thesis, a simple, accurate, cost-effective predictive tool is not currently available. Future studies should observe the cost-effectiveness of this and other interventions aimed at reducing the risk of stroke recurrence after initial stroke.

8.6 Summary

This thesis demonstrated that the risk of stroke recurrence after first stroke is considerable, up to 25% at 12 years after first stroke. Cardiovascular risk factors are important predictors of stroke recurrence however further research is needed to explore the association between secondary prevention and risk of stroke recurrence. Stroke recurrence was shown to be associated with increased risk of death at all time-points up to 15 years after first stroke. Recurrence in the first year after stroke was associated with the biggest increase in risk of death, identifying a potentially important time-period for both stroke management and future research to be targeted

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Appendices

Appendix 1. Publications arising from this thesis

PAPERS

Mohan KM, Crichton SL, Grieve AP, Rudd AG, Wolfe CD, Heuschmann PU. Frequency and Predictors for the risk of stroke recurrence up to 10 years after stroke: the South London Stroke Register. JNNP 2009; 80(9): 1012-8.

Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and Cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke 2011; 42(5): 1489-94.

Addo J, Ayerbe L, Mohan K, Crichton S, Sheldenkar A, Chen R, Wolfe CDA, McKevitt C. Socioeconomic status and stroke- an updated review. Stroke. 2012;43(4):1186-91.

PRESENTATIONS

Mohan KM, Crichton SL, Grieve AP, Rudd AG, Wolfe CDA, Heuschmann PU. Very long term risk of stroke recurrence. World Stroke Congress Vienna. 2008. Oral presentation.

Mohan KM, Grieve AP, Heuschmann PU, Rudd AG, Wolfe CDA. Stroke recurrence after first-ever stroke: a systematic review of literature. UK Stroke Forum Glasgow. 2009. Oral presentation.

Mohan KM, Grieve AP, Heuschmann PU, Rudd AG, Wolfe CDA. Differences in risk of stroke recurrence after first-ever stroke: a systematic review and meta-analysis. European Stroke Conference Barcelona 2010. Oral presentation.

Mohan KM, Grieve AP, Rudd AG, Heuschmann PU, Wolfe CDA. Differences in stroke subtype between first-ever and recurrent stroke: the South London Stroke Register (SLSR). European Stroke Conference Hamburg 2011. Poster presentation.

Appendix 2. South London Stroke Register (SLSR) documentation

(i) SLSR INITIAL FORM

(ii) SLSR RECURRENCE FORM

(iii) SLSR ANNUAL FOLLOW-UP FORM

(iv) SLSR PATIENT CONSENT FORM

Draft

SOUTH LONDON STROKE REGISTER

ID Number

INITIAL FORM V19

Interviewer ID

1. Date of interview

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year : 2011 2012 2013 2014 2015

NOTIFICATION DETAILS

2. Date of notification

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year : 2008 2009 2010 2011 2012 2013

3. Notification Sources

Please select ALL relevant answers

- 1. GP and practice staff
- 2. Ambulance doctors
- 3. Practice computer records
- 4. Hospital staff
- 5. Hospital computer records
- 6. Radiology records
- 7. Accident and Emergency
- 8. Community therapists
- 9. Post mortems
- 10. Coroner's records
- 11. Death certificates
- 12. Research teams/ward checks
- 13. Bereavement officer
- 14. Bed manager
- 15. Nursing home
- 16. Neurovascular clinic
- 17. Other *Specify:*

4. Primary source of notification:

SOCIODEMOGRAPHIC DETAILS

5. Date of Birth

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: 1800 / 1900 / 2000 0 1 2 3 4 5 6 7 8 9

6. Sex

Male Female

7a. Ethnic Group

Information to be obtained directly from patient.

White
- British
- Irish
- Other White background

Mixed
- White and Black Caribbean
- White and Black African
- Other mixed background
- White and Asian

Other ethnic categories
- Chinese
- Any other ethnic category

Black or Black British
- Caribbean
- African
- Other Black background

Asian or British Asian
- Bangladeshi
- Indian
- Pakistani
- Other Asian background

Not stated
- Not stated

7b. Was the patient born in the UK?

- Yes → Go to question 7d
- No
- Unknown → Go to question 7d

7c. Country of Birth of Patient

7d. Country of Birth of Patient's Father

7e. Country of Birth of Patient's Mother

8. Living Conditions Prior to Stroke

- Private household alone
- Private household with others
- Sheltered home
- Residential home
- Nursing home
- Community hospital
- Private hospital
- Long term hospital care
- Unknown
- Other *Specify:*

9a. In the last 2 weeks, has the patient required help from another person for everyday activities (such as making a cup of tea)?

- Yes
- No → Go to question 10
- Unknown → Go to question 10

9b. If yes, who did the patient receive most help from? (select one)

- Home help or carer
- Spouse/partner
- Daughter
- Other *Specify*
- Son
- Other relative
- Other professional care (paid/unpaid)
- Unknown
- Friend
- Voluntary Organisation

10. Patient's Education Level

Information to be obtained directly from patient.

- No formal education
- Primary
- Lower secondary
- Upper secondary
- Post secondary non tertiary
- First stage of tertiary
- Secondary stage of tertiary
- Unknown

11. Employment Status Prior to Stroke

- Full time employed *(more than 30hrs/wk)*
- Part time employed *(less than 30hrs/wk)*
- Retired
- Unknown
- Carer for home/family/dependents
- Unemployed and looking for work
- Unable to work due to disability/ill-health

Draft

SOUTH LONDON STROKE REGISTER

ID Number

INITIAL FORM V19

Interviewer ID

1. Date of interview

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

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Please select ALL relevant answers

- 1. GP and practice staff
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- 8. Community therapists
- 9. Post mortems
- 10. Coroner's records
- 11. Death certificates
- 12. Research teams/ward checks
- 13. Bereavement officer
- 14. Bed manager
- 15. Nursing home
- 16. Neurovascular clinic
- 17. Other *Specify:*

4. Primary source of notification:

SOCIODEMOGRAPHIC DETAILS

5. Date of Birth

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: 1800 / 1900 / 2000 0 1 2 3 4 5 6 7 8 9

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Male Female

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Information to be obtained directly from patient.

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- Other White background

Mixed
- White and Black Caribbean
- White and Black African
- Other mixed background
- White and Asian

Other ethnic categories
- Chinese
- Any other ethnic category

Black or Black British
- Caribbean
- African
- Other Black background

Asian or British Asian
- Bangladeshi
- Indian
- Pakistani
- Other Asian background

Not stated
- Not stated

7b. Was the patient born in the UK?

- Yes → Go to question 7d
- No
- Unknown → Go to question 7d

7c. Country of Birth of Patient

7d. Country of Birth of Patient's Father

7e. Country of Birth of Patient's Mother

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- Private household alone
- Private household with others
- Sheltered home
- Residential home
- Nursing home
- Community hospital
- Private hospital
- Long term hospital care
- Unknown
- Other *Specify:*

9a. In the last 2 weeks, has the patient required help from another person for everyday activities (such as making a cup of tea)?

- Yes
- No → Go to question 10
- Unknown → Go to question 10

9b. If yes, who did the patient receive most help from? (select one)

- Home help or carer
- Spouse/partner
- Daughter
- Other *Specify*
- Son
- Other relative
- Other professional care (paid/unpaid)
- Unknown
- Friend
- Voluntary Organisation

10. Patient's Education Level

Information to be obtained directly from patient.

- No formal education
- Primary
- Lower secondary
- Upper secondary
- Post secondary non tertiary
- First stage of tertiary
- Secondary stage of tertiary
- Unknown

11. Employment Status Prior to Stroke

- Full time employed *(more than 30hrs/wk)*
- Part time employed *(less than 30hrs/wk)*
- Retired
- Unknown
- Carer for home/family/dependents
- Unemployed and looking for work
- Unable to work due to disability/ill-health

12. Patient's Occupation (Please insert most recent occupation)

13. Employment status (in most recent occupation)

- ☐ Self-employed with 25 or more employees
- ☐ Self-employed with less than 25 employees
- ☐ Self-employed with no employees
- ☐ Manager in establishment with 25 or more employees
- ☐ Manager in establishment with less than 25 employees
- ☐ Supervisor
- ☐ Employee
- ☐ Unknown

RISK FACTORS PRIOR TO STROKE

14a. Is there a recent GP/hospital BP record prior to stroke?

☐ Yes

☐ No → Go to question 15

☐ Unknown → Go to question 15

14b. What was the recorded BP?

SBP ☐☐☐ DBP ☐☐☐

14c. What date was the BP recorded?

Day: 10 20 30 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Year: 1990 2000 2010 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9

15. Is there a recent GP/hospital record ofany of the following diagnosis prior to stroke?

Hypertension	☐ Yes	☐ No	☐ Unknown
Congestive Cardiac Failure	☐ Yes	☐ No	☐ Unknown
Angina	☐ Yes	☐ No	☐ Unknown
Hypercholesterolaemia	☐ Yes	☐ No	☐ Unknown
Peripheral vascular disease	☐ Yes	☐ No	☐ Unknown
Oral Contraceptive pill (in last 6 months)	☐ Yes	☐ No	☐ Unknown
Sickle cell disease	☐ Yes	☐ No	☐ Unknown
Migraine	☐ Yes	☐ No	☐ Unknown
Atrial fibrilation	☐ Yes	☐ No	☐ Unknown
TIA	☐ Yes	☐ No	☐ Unknown
Depression	☐ Yes	☐ No	☐ Unknown

16a. Is there a recent GP/hospital record of Myocardial Infarction (MI) prior to stroke?

☐ Yes

☐ No → Go to question 17

☐ Unknown → Go to question 17

16b. How long ago was the MI?

- ☐ <1 month ago
- ☐ 1-6 months ago
- ☐ over 6 months ago

17a. Was the patient diabetic prior to stroke?

☐ Yes, on insulin ☐ Yes, on oral hypoglycaemics

☐ Yes, diet control only ☐ Yes, on insulin and oral hypoglycaemics

☐ No → Go to question 18

☐ Unknown → Go to question 18

17b. Is the last HbA1c prior to stroke known?

☐ Yes

☐ No → Go to question 18

☐ Unknown → Go to question 18

17c. What was the last HbA1c? ☐☐.☐

18a. Is there a family history of vascular diseases, such as stroke or MI, in the patient's biological family (i.e. biological father, biological mother or siblings)?

☐ Yes

☐ No → Go to question 19

☐ Unknown → Go to question 19

18b. If yes:

	Stroke	Age at first stroke	MI	Age at first MI
Father	☐ No ☐ Yes ☐ Unknown	☐☐☐	☐ No ☐ Yes ☐ Unknown	☐☐☐
Mother	☐ No ☐ Yes ☐ Unknown	☐☐☐	☐ No ☐ Yes ☐ Unknown	☐☐☐
Sibling	☐ No ☐ Yes ☐ Unknown	☐☐☐	☐ No ☐ Yes ☐ Unknown	☐☐☐

If there is a history of stroke in one or more siblings, please enter the youngest age at which an event occured in ANY sibling. Similarly, where there is a history of MI, please insert the youngest age at which there was an event.

Draft

SOUTH LONDON STROKE REGISTER ID Number

INITIAL FORM V19

19a. Does the patient smoke?

- ☐ Current smoker → Go to question 19c
- ☐ Ex-Smoker
- ☐ Never smoked → Go to question 20
- ☐ Unknown → Go to question 20

19b. If an ex-smoker, when did the patient give up?

Month: ☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sept ☐ Oct ☐ Nov ☐ Dec

Year: ☐ 1900 ☐ 2000 ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9

19c. How old was the patient when they started smoking?

☐☐☐ years

19d. How much did/does the patient smoke a day?

Cigarettes (number) ☐☐☐

Tobacco (grams) ☐☐

Cigars (number) ☐☐

20a. Does the patient drink any alcohol?

- ☐ Yes
- ☐ No → Go to question 21
- ☐ Unknown → Go to question 21

20b. How much does the patient drink a week?

Beer (pints) ☐☐☐ Wine (glasses) ☐☐☐

Spirits (glasses) ☐☐☐

N.B. If the patient is an occassional drinker and drinks less than one unit per week, enter '0' in each of the three categories.

21a. How was the patient's weight obtained?

- ☐ Measured
- ☐ Recalled by patient
- ☐ Estimated
- ☐ Unknown → Go to question 21c
- ☐ Not done → Go to question 21c

21b. Patient's weight (k.g.) ☐☐☐.☐

21c. Patient's height (m) ☐.☐☐

MEDICATIONS PRIOR TO STROKE

22. Was the patient taking any regular medication in the month prior to stroke?

- ☐ Yes
- ☐ No → Go to question 24
- ☐ Unknown → Go to question 24

23. List all medications: (Generic Name)

	Name	Dose			Frequency		
A.		☐☐☐☐.☐☐	☐ mg ☐ mcg ☐ ml	☐ units ☐ puffs ☐ other	☐ 1x ☐ 2x ☐ 3x ☐ 4x ☐ >4x	☐ Daily ☐ Weekly ☐ Variable ☐ Other	
B.		☐☐☐☐.☐☐	☐ mg ☐ mcg ☐ ml	☐ units ☐ puffs ☐ other	☐ 1x ☐ 2x ☐ 3x ☐ 4x ☐ >4x	☐ Daily ☐ Weekly ☐ Variable ☐ Other	
C.		☐☐☐☐.☐☐	☐ mg ☐ mcg ☐ ml	☐ units ☐ puffs ☐ other	☐ 1x ☐ 2x ☐ 3x ☐ 4x ☐ >4x	☐ Daily ☐ Weekly ☐ Variable ☐ Other	
D.		☐☐☐☐.☐☐	☐ mg ☐ mcg ☐ ml	☐ units ☐ puffs ☐ other	☐ 1x ☐ 2x ☐ 3x ☐ 4x ☐ >4x	☐ Daily ☐ Weekly ☐ Variable ☐ Other	
E.		☐☐☐☐.☐☐	☐ mg ☐ mcg ☐ ml	☐ units ☐ puffs ☐ other	☐ 1x ☐ 2x ☐ 3x ☐ 4x ☐ >4x	☐ Daily ☐ Weekly ☐ Variable ☐ Other	

Draft

SOUTH LONDON STROKE REGISTER ID Number

INITIAL FORM V19

	Name	Dose		Frequency	
F.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
G.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
H.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
I.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
J.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
K.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
L.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
M.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
N.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other
O.		.	☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Weekly ☐ Variable ☐ Other

N.B. If there are more than 15 medications, use 'extra medications' form and attach to back of this questionnaire.

STROKE ONSET AND SYMPTOMS

24. Date of stroke onset

Day: 10 20 30 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

25a. Time of first stroke symptom (24hr clock) h h : m m

25b. Is the time of stroke definite?

☐ Yes → Go to question 26

☐ No

☐ Unknown → Go to question 26

25c. If no, did the patient wake up with the stroke?

☐ Yes

☐ No

☐ Unknown

26. Was the patient already in hospital at the time of stroke?

☐ Yes → Go to question 29

☐ No

☐ Unknown

27a. Was the patient seen in A&E?

☐ Yes

☐ No → Go to question 28

☐ Unknown → Go to question 28

27b. Date of arrival in A&E of first hospital .

Day: ☐ 10 ☐ 20 ☐ 30 ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9

Month: ☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sept ☐ Oct ☐ Nov ☐ Dec

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

27c. Time of arrival in A&E (24hr clock) h h : m m

28. Was the patient admitted to hospital?

☐ Yes

☐ No

☐ Unknown

STROKE SEVERITY (at time of maximum impairment)

29a. Is the level of consciousness (Glasgow Coma Scale) known?

☐ Yes

☐ No → Go to question 30

☐ Unknown → Go to question 30

29b. What was the GCS?

Eye

☐ 1 no eye opening

☐ 2 eye opening to pain

☐ 3 eye opening to speech

☐ 4 spontaneous eye opening

Verbal

☐ 1 None

☐ 2 Incomprehensible words

☐ 3 inappropriate wrods

☐ 4 confused conversation

☐ 5 orientated

Motor

☐ 1 No response

☐ 2 Extension to pain

☐ 3 abnormal flexor response to pain

☐ 4 withdraws from pain

☐ 5 localising response

☐ 6 obeying commands

30a. Swallow test results (by formal assessment)

☐ Fail

☐ Pass

☐ Not assessed → Go to question 31

30b. If *admitted*, was the test done within 24hrs post stroke admission?

☐ Yes → Go to question 31

☐ No → Go to question 31

☐ Unknown → Go to question 31

30c. If *not admitted*, was it done within 24hrs post stroke?

☐ Yes

☐ No

☐ Unknown

31. Has the patient been incontinent since the stroke?

☐ Yes

☐ No

☐ Unknown

32. Is the patient able to lift both arms to the horizontal?
(MRC score>2 in both arms)

☐ Yes

☐ No

☐ Unknown

33. Is the patient able to walk without the help of another person (can use stick/frame)?

☐ Yes

☐ No

☐ Unknown

34. Is the patient literate?

! *Information to be obtained directly from patient.* !

☐ Yes

☐ No

☐ Unknown

35. Is the patient right or left handed?

! *Information to be obtained directly from patient.* !

☐ Left

☐ Right

☐ Unknown

36.Stroke subtype

☐ Cerebral Infarction ☐ SAH

☐ PICH ☐ Undefined

Subtype should be defined by brain imaging, lumbar puncture (SAH only) or postmortem autopsy. If none of these investigations were performed, stroke subtype must be recorded as undefined

SOUTH LONDON STROKE REGISTER ID Number

INITIAL FORM V19

37. BARTHEL INDEX

	37a. Pre-Stroke status as at day before stroke	37b. Post-Stroke document status at day 5-10 or on discharge
	☐ Done ☐ Not done → Go to 37b ☐ Unknown → Go to 37b	☐ Done ☐ Not done → Go to 38 ☐ Unknown → Go to 38
FEEDING 0=unable 5=needs help cutting, spreading butter, etc., or requires modified diet 10=independent	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10
BATHING 0 = dependent 5 = independent (or in shower)	☐ 0 ☐ 5	☐ 0 ☐ 5
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	☐ 0 ☐ 5	☐ 0 ☐ 5
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10
TOILET 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	☐ 0 ☐ 5 ☐ 10 ☐ 15	☐ 0 ☐ 5 ☐ 10 ☐ 15
MOBILITY (ON LEVEL SURFACES) 0=immobile or <50 yards 5=wheelchair independent, including corners, >50 yards 10=walks with the help of one person (verbal or physical) >50 yards 15=independent (but may use any aid; for example, stick) >50 yards	☐ 0 ☐ 5 ☐ 10 ☐ 15	☐ 0 ☐ 5 ☐ 10 ☐ 15
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	☐ 0 ☐ 5 ☐ 10	☐ 0 ☐ 5 ☐ 10

38. NIH STROKE SCALE

Document at time of maximum impairment

☐ Done
☐ Not done → Go to question 39
☐ Unknown → Go to question 39

1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	☐ 0 ☐ 1 ☐ 2 ☐ 3	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	☐ 0 ☐ 1 ☐ 2	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	☐ 0 ☐ 1 ☐ 2	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	☐ 0 ☐ 1 ☐ 2	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	☐ 0 ☐ 1 ☐ 2 ☐ 3	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	☐ 0 ☐ 1 ☐ 2 ☐ 3	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	RIGHT ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ UN LEFT ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ UN	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion

6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	RIGHT ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ UN LEFT ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ UN	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	☐ 0 ☐ 1 ☐ 2	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs.
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	☐ 0 ☐ 1 ☐ 2	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	☐ 0 ☐ 1 ☐ 2 ☐ 3	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	☐ 0 ☐ 1 ☐ 2 ☐ UN	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier.
11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	☐ 0 ☐ 1 ☐ 2	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.

39. MEMORY TESTING

☐ Done
☐ Not done → Go to question 40
☐ Unknown → Go to question 40

Document at 5-10 days post-stroke or on discharge

! *Information to be obtained directly from patient.* !

	Does patient answer correctly?	
1. How old are you?	☐ Yes	☐ No
2. What is the time (to the nearest hour, without looking at a clock)?	☐ Yes	☐ No
3. Please remember this address, you will be tested on it later on: ***42 West St.*** (the patient should recall the address to ensure it is heard correctly and then be tested on it in 5 minutes time; all parts must be recalled)	☐ Yes	☐ No
4. Which year are we in?	☐ Yes	☐ No
5. What is the name of the district that you are in?	☐ Yes	☐ No
6. a) What is my job? (You must ensure that you informed the patient initially) b) Can you name this object? (eg. a watch / pen / glasses) **(both parts must be answered correctly to score a point)**	☐ Yes	☐ No
7. What is your date of birth?	☐ Yes	☐ No
8. What was the date of the Second World War?	☐ Yes	☐ No
9. Can you name the present Monarch (Queen) ?	☐ Yes	☐ No
10. Can you start at 20 and count backwards?	☐ Yes	☐ No

Did the patient remember the address? (fill in question 3)

ACUTE INTERVENTIONS

40a.Was the patient on antiplatelet therapy in the first 14 days after stroke?
☐ Yes
☐ No
☐ Unknown

40b. If yes, which kind?

Aspirin	☐ Yes	☐ No ☐ Unknown → Go to question 41	
Clopidogrel	☐ Yes	☐ No ☐ Unknown → Go to question 41	
Other	☐ Yes	☐ No ☐ Unknown → Go to question 41	

40c.If yes, was it given within 48hrs?
☐ Yes
☐ No
☐ Unknown

41a. Was the patient on anticoagulant drugs in the first 14 days after stroke?
☐ Yes
☐ No → Go to question 42
☐ Unknown → Go to question 42

41b.If yes, which types?

Oral	Intravenous	Subcutaneous
☐ Yes	☐ Yes	☐ Yes
☐ No	☐ No	☐ No
☐ Unknown	☐ Unknown	☐ Unknown

42.Was the patient given cholesterol lowering drugs in the first 14 days after stroke?
☐ Yes
☐ No
☐ Unknown

43a. Did the patient receive thrombolysis?
☐ Yes
☐ No → Go to question 44
☐ Unknown → Go to question 44

43b.If yes, which methods?

Intravenous	Intraarterial
☐ Yes	☐ Yes
☐ No	☐ No
☐ Unknown	☐ Unknown

44.Was the patient given intravenous fluids in the first 14 days after stroke?
☐ Yes
☐ No
☐ Unknown

45. Naso-gastric or PEG feeding in the first 14 days after stroke?
☐ Yes
☐ No
☐ Unknown

DISCHARGE INFORMATION

If the patient is still in hospital more than two weeks post stroke, please retain pages 10-12 for completion following discharge and return the rest of the form, complete, to the Stroke Office with the confidential discharge sheet.

46.Were any of the following interventional procedures done for the stroke? *Please select ALL relevant*

Stent	☐ Yes	☐ No	☐ Unknown
Coil	☐ Yes	☐ No	☐ Unknown
Tracheostomy	☐ Yes	☐ No	☐ Unknown
Evacuation	☐ Yes	☐ No	☐ Unknown
Craniectomy	☐ Yes	☐ No	☐ Unknown
Carotid Endarterectomy	☐ Yes	☐ No	☐ Unknown
Other	☐ Yes	☐ No	☐ Unknown

47. Was the patient seen by?

	1=No	2=Once	3=More than once	4=Unknown
Specialist physician in stroke medicine	☐ 1	☐ 2	☐ 3	☐ 4
Dietician	☐ 1	☐ 2	☐ 3	☐ 4
Psychologist	☐ 1	☐ 2	☐ 3	☐ 4
Social worker	☐ 1	☐ 2	☐ 3	☐ 4
Speech and language therapist	☐ 1	☐ 2	☐ 3	☐ 4
Occupational therapist	☐ 1	☐ 2	☐ 3	☐ 4
Physiotherapist	☐ 1	☐ 2	☐ 3	☐ 4

48. Since the stroke, has the patient been diagnosed with any of the following?

Hypertension	☐ No	☐ Yes	☐ Unknown
High Cholesterol	☐ No	☐ Yes	☐ Unknown
Atrial Fibrillation	☐ No	☐ Yes	☐ Unknown
Diabetes	☐ No	☐ Yes	☐ Unknown
Myocardial Infarction	☐ No	☐ Yes	☐ Unknown

BED MOVEMENTS

49ai. Date of admission to first ward

Day: ☐☐ (10 20 30) ☐☐ (0 1 2 3 4 5 6 7 8 9)

Month: ☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sept ☐ Oct ☐ Nov ☐ Dec

Year ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

Hospital ☐ STH ☐ KCH ☐ STG ☐ UCLH ☐ LEW ☐ Other *Specify:* _____

49aii. Time of admission to first ward (24hr clock) ☐☐☐☐

49aiii. Type of ward first admitted to

☐ Acute medical ☐ Surgery ☐ Neurosurgery ☐ Other
☐ Geriatric ☐ Acute Stroke Unit ☐ Private
☐ ITU/HDU ☐ Rehab Stroke Unit ☐ Generic Rehab Unit

49bi. Date of admission to second ward

Day: ☐☐ (10 20 30) ☐☐ (0 1 2 3 4 5 6 7 8 9)

Month: ☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sept ☐ Oct ☐ Nov ☐ Dec

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

Hospital ☐ STH ☐ KCH ☐ STG ☐ UCLH ☐ LEW ☐ Other *Specify:* _____

49bii. Second ward type

☐ Acute medical ☐ Surgery ☐ Neurosurgery ☐ Other
☐ Geriatric ☐ Acute Stroke Unit ☐ Private
☐ ITU/HDU ☐ Rehab Stroke Unit ☐ Generic Rehab Unit

49ci. Date of admission to third ward

Day: ☐☐ (10 20 30) ☐☐ (0 1 2 3 4 5 6 7 8 9)

Month: ☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sept ☐ Oct ☐ Nov ☐ Dec

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

Hospital ☐ STH ☐ KCH ☐ STG ☐ UCLH ☐ LEW ☐ Other *Specify:* _____

49cii. Third ward type

☐ Acute medical ☐ Surgery ☐ Neurosurgery ☐ Other
☐ Geriatric ☐ Acute Stroke Unit ☐ Private
☐ ITU/HDU ☐ Rehab Stroke Unit ☐ Generic Rehab Unit

49di. Date of admission to fourth ward

Day: ☐☐ (10 20 30) ☐☐ (0 1 2 3 4 5 6 7 8 9)

Month: ☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sept ☐ Oct ☐ Nov ☐ Dec

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

Hospital ☐ STH ☐ KCH ☐ STG ☐ UCLH ☐ LEW ☐ Other *Specify:* _____

49dii. Fourth ward type

☐ Acute medical ☐ Surgery ☐ Neurosurgery ☐ Other
☐ Geriatric ☐ Acute Stroke Unit ☐ Private
☐ ITU/HDU ☐ Rehab Stroke Unit ☐ Generic Rehab Unit

49ei. Date of admission to fifth ward

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

Hospital: STH KCH STG UCLH LEW Other *Specify:* _____

49eii. Fifth ward type

☐ Acute medical ☐ Surgery ☐ Neurosurgery ☐ Other
☐ Geriatric ☐ Acute Stroke Unit ☐ Private
☐ ITU/HDU ☐ Rehab Stroke Unit ☐ Generic Rehab Unit

49fi. Date of admission to sixth ward:

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

Hospital: STH KCH STG UCLH LEW Other *Specify:* _____

49fii. Sixth ward type

☐ Acute medical ☐ Surgery ☐ Neurosurgery ☐ Other
☐ Geriatric ☐ Acute Stroke Unit ☐ Private
☐ ITU/HDU ☐ Rehab Stroke Unit ☐ Generic Rehab Unit

DISCHARGE

50a. Date of discharge or death

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

Hospital: STH KCH STG UCLH LEW Other *Specify:* _____

50b. Discharge destination

☐ Private household alone ☐ Nursing home ☐ Residential home
☐ Private household with carer ☐ Private hospital ☐ Death
☐ Sheltered home ☐ Community hospital ☐ Other
☐ Long term hospital care

51a. Did a stroke recurrence occur before discharge?

☐ Yes
☐ No → Go to question 52
☐ Unknown → Go to question 52

51b. Date of first recurrence

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

51c. Date of second recurrence

Day: 10 20 30 0 1 2 3 4 5 6 7 8 9

Month: Jan Feb Mar Apr May Jun Jul Aug Sept Oct Nov Dec

Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

52a. Did the patient receive any drugs as part of a trial?

☐ Yes
☐ No → Go to question 53
☐ Unknown → Go to question 53

52b. If yes, specify:

MEDICATIONS AT DISCHARGE

53. List all medications prescribed on discharge or since stroke for non-admitted patients: (Generic Name)

	Name of drug	Dose		Frequency	
A.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
B.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
C.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
D.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
E.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
F.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
G.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
H.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
I.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
J.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
K.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
L.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
M.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
N.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable
O.			☐ mg ☐ units ☐ mcg ☐ puffs ☐ ml ☐ other	☐ 1x ☐ 4x ☐ 2x ☐ >4x ☐ 3x	☐ Daily ☐ Other ☐ Weekly ☐ Variable

N.B. If there are more than 15 medications, use 'extra medications' form and attach to back of this questionnaire.

Draft

SOUTH LONDON STROKE REGISTER

ID Number

INITIAL FORM V19

Interviewer ID

ECG

1a. Was an ECG performed?

☐ Yes

☐ No → Go to question 2

☐ Unknown → Go to question 2

1b. If yes was there any sustained arrythmia?

☐ Yes

☐ No → Go to question 2

☐ Unknown → Go to question 2

1c. If yes, what type?

☐ Atrial Fibrillation ☐ Sick sinus syndrome

☐ Atrial flutter ☐ Other

ECHO

2a. Was an ECHO performed?

☐ Yes → Go to question 2c

☐ No

☐ Unknown → Go to question 3

2b. If no, what was the reason?

☐ Haemorrhage ☐ Refused ☐ Not indicated

☐ Died ☐ Other *Specify:* Go to question 3

☐ Unable to contact

2c. If yes, what type?

☐ TTE ☐ Post mortem

☐ TOE ☐ Unknown

2d. If an ECHO was performed, were there any abnormal findings?

☐ Yes

☐ No → Go to question 3

☐ Unknown → Go to question 3

Please specify,

LA/atrial appendage thrombus	☐ No	☐ Yes	☐ Unknown	
Atrial myxoma	☐ No	☐ Yes	☐ Unknown	
Atrial septum aneurysum	☐ No	☐ 10-15mm	☐ >15mm	☐ Unknown
Patent foramen ovale	☐ No	☐ <5 bubbles	☐ 5-20 bubbles	☐ >20 bubbles ☐ Unknown
LVEF	☐ No	☐ <30%	☐ 30-50%	☐ >50% ☐ Unknown
LV thrombus	☐ No	☐ Mobile	☐ Non-mobile	☐ Unknown
Dilated cardiomyopathy	☐ No	☐ Yes	☐ Unknown	
LV segment	☐ Normal	☐ Akinetic	☐ Hypokinetic/Dyskinetic	☐ N/A ☐ Unknown
Nonbacterial thrombotic endocarditis	☐ No	☐ Yes	☐ Unknown	
Infective endocarditis	☐ No	☐ Yes	☐ Unknown	
Mechanical prosthetic valve	☐ No	☐ Aortic	☐ Mitral	☐ Unknown
Bioprosthetic valve	☐ No	☐ Aortic	☐ Mitral	☐ Unknown

VASCULAR IMAGING OF BRAIN SUPPLYING ARTERIES

3a. Were any vascular imaging tests perfomed?

☐ Yes → Go to question 3c

☐ No

☐ Unknown → Go to question 4

3b. If no, what was the reason?

☐ N/A ☐ Refused ☐ Not indicated

☐ Died ☐ Other *Specify:* Go to question 4

☐ Unable to contact

3c. If yes, which ones?

Please select ALL relevant answers

☐ Doppler ultrasound ☐ MRA

☐ CTA ☐ Transcranial doppler

☐ Angiogram ☐ Other *Specify:*

☐ Duplex

3d. Was a relevant stenosis of the vessel(s)

☐ Yes

☐ No → Go to question 4

☐ Unknown → Go to question 4

3e. If yes, please document the estimated degree of stenosis as a percentage of the vessel(s)

R CCA	%	L CCA	%
R ICA	%	L ICA	%
R MCA	%	L MCA	%
R Posterior Circulation	%	L Posterior Circulation	%

3f. Other results of angiology

Please select ALL relevant answers

☐ Dissection ☐ None

☐ Intracranial stenosis ☐ Other *Specify:*

☐ AVM

☐ Aneurysm

BLOOD INVESTIGATIONS

4a. Patients total cholesterol level

☐ Not done

☐ Unknown *state value* .

4b. Patients glucose level

☐ Not done

☐ Unknown *state value* .

4c. HbS (BLACK AFRICAN AND CARRIBEAN PATIENTS ONLY)

☐ Not present ☐ Not done
☐ Trait ☐ Unknown
☐ Heterozygous ☐ N/A

BRAIN IMAGING

5a. Were any of the following scans done?

	No	Yes, one	Yes, two	Yes, three	Yes, more than three	Unknown
CT	☐	☐	☐	☐	☐	☐
MRI	☐	☐	☐	☐	☐	☐
Angiography	☐	☐	☐	☐	☐	☐

5b. Date of first CT scan

Day: ☐☐ (10 20 30 / 0 1 2 3 4 5 6 7 8 9)
Month: ☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sept ☐ Oct ☐ Nov ☐ Dec
Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

5c. Date of first MRI scan

Day: ☐☐ (10 20 30 / 0 1 2 3 4 5 6 7 8 9)
Month: ☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sept ☐ Oct ☐ Nov ☐ Dec
Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

5d. Date of first angiography

Day: ☐☐ (10 20 30 / 0 1 2 3 4 5 6 7 8 9)
Month: ☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sept ☐ Oct ☐ Nov ☐ Dec
Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

RESULTS OF BRAIN IMAGING

6a. Localisation of stroke

☐ Location based on clinical signs ☐ No definite location
☐ Location based on imaging ☐ Unknown

	Right	Left	Both	Unknown
6b. ACA				
Cortex	☐	☐	☐	☐
6c MCA				
Cortex	☐	☐	☐	☐
Basal ganglia	☐	☐	☐	☐
6d. Posterior Circulation				
Cortex	☐	☐	☐	☐
Thalamus	☐	☐	☐	☐
Brainstem	☐	☐	☐	☐
Cerebellum	☐	☐	☐	☐

RESULTS OF 1st BRAIN IMAGING AFTER STROKE

7a. Estimated size of the lesion (when multiple lesions are present enter the size of the largest).

☐ No lesions ☐ 0.3-1.5cm ☐ Unknown
☐ <0.3cm ☐ >1.5cm

7b. Multiple lesions?

☐ No ☐ 2-4 ☐ >4 ☐ Unknown

7c. White matter lesions

☐ Yes ☐ No ☐ Unknown

RESULTS OF MOST RELEVANT DIAGNOSTIC SCAN

8a. Type of most relevant diagnostic scan?

☐ CT ☐ MRI ☐ Unknown

8b. Estimated size of the lesion (when multiple lesions are present enter the size of the largest).

☐ No lesions ☐ 0.3-1.5cm ☐ Unknown
☐ <0.3cm ☐ >1.5cm

8c. Multiple lesions?

☐ No ☐ 2-4 ☐ >4 ☐ Unknown

8d. White matter lesions

☐ Yes ☐ No ☐ Unknown

9. Date of most relevant diagnostic scan

Day: ☐☐ (10 20 30 / 0 1 2 3 4 5 6 7 8 9)
Month: ☐ Jan ☐ Feb ☐ Mar ☐ Apr ☐ May ☐ Jun ☐ Jul ☐ Aug ☐ Sept ☐ Oct ☐ Nov ☐ Dec
Year: ☐ 2008 ☐ 2009 ☐ 2010 ☐ 2011 ☐ 2012 ☐ 2013

STROKE CLASSIFICATION

10. OCSP Classification

☐ TACI ☐ LACI ☐ SAH
☐ PACI ☐ Infaction unspecified ☐ Unclassified
☐ POCI ☐ PICH ☐ Unknown

11. TOAST Classification (ISCHAEMIC STROKE ONLY)

Large artery atherosclerosis
☐ Extra-cranial
☐ Intra-cranial
Cardio-embolic
☐ High risk
☐ Medium risk
Small vessel occlusion
☐ Small vessel occlusion
Undetermined
☐ No aetiology identified
☐ Multiple probable aetiologies
Other determined
☐ Vasculopathy
☐ Haemoglobinopathy
☐ Hypercoagulable state
☐ Migrainious
☐ Other
Specify: _____

12. Modified TOAST Classification (ISCHAEMIC STROKE ONLY)

Large artery atherosclerosis
☐ Extra-cranial
☐ Intra-cranial
Cardio-embolic
☐ High risk
☐ Medium risk
Small vessel occlusion
☐ Small vessel occlusion
Undetermined
☐ No aetiology identified
☐ Multiple probable aetiologies
Other determined
☐ Vasculopathy
☐ Haemoglobinopathy
☐ Hypercoagulable state
☐ Migrainious
☐ Other
Specify: _____

(iii) SLSR FOLLOW UP FORM

SOUTH LONDON STROKE REGISTER

ANNUAL FOLLOW UP

Thank you for taking time to complete this questionnaire. It will help us to know how you are getting on since your stroke.

Please read the following guidelines before beginning.

Answer all questions. We are well aware that some questions might not seem relevant to you personally, but please try to answer them all as best you can.

You should complete the form yourself, however if you are unable to then a carer or relative may help you.

Most questions require you to select your answer from choices given to you by selecting the box beside the *one* choice which best describes your situation /feelings.

1. What is today's date? Click here to enter a date.

---

2. What is your date of birth? Click here to enter a date.

---

3. Where do you live?

☐Private household alone ☐Community hospital

☐Private household with others ☐Private hospital

☐Sheltered home ☐Long term hospital care

☐Residential home ☐Other

☐Nursing home *Specify:* Click here to enter text.

---

4. What is your current employment status?

☐Full time employed *(more than 30hrs/wk)*

☐Part time employed *(less than 30hrs/wk)*

☐Unemployed and looking for work

☐Retired

☐Unable to work due to disability/ill-health

☐Carer for home/family/dependents

5a. Have you had another stroke in the last year?

☐Yes ☐No ☐I don't know

5b.Have you been readmitted to hospital since the last follow up?

☐Yes ☐No →Go to question 6

5c.What was the name of the hospital?

Click here to enter text.

5d. Were you in hospital because you had had another stroke?

☐Yes ☐No ☐I don't know

---

6. In the last year have you experienced any of the following symptoms?

a. New visual problems ☐Yes ☐No ☐I don't know

c. New weakness of arms/legs ☐Yes ☐No ☐I don't know

b. New speech problems ☐Yes ☐No ☐I don't know

6d.If yes to any of the above, did you see your GP about the new symptoms?

☐Yes ☐No

7a. In the last 2 weeks, have you required help from another person for everyday activities (such as making a cup of tea)?

☐Yes ☐No →Go to question

7b. If yes, who did you receive most help from?

☐Home help or carer

☐Spouse/partner

☐Daughter

☐Son

☐Other relative

☐Friend

☐Voluntary Organisation

☐Other professional care (paid/unpaid)

☐Other- Specify*:* Click here to enter text.

8. Has a member of your family given up work since the stroke to care for you?

☐Yes ☐No

---

9. Are you still in hospital, a nursing home, or a residential home?

☐Yes →Go to question 17 ☐ No

---

10. Do your friends and family help you (at least once a week) with any of the following?

a. Cleaning the house ☐ Yes ☐No

b. Preparing meals ☐ Yes ☐No

c. Shopping ☐ Yes ☐No

d. Having a bath or shower ☐ Yes ☐No

---

11. In the last week have you had any meals on wheels?

How many times?

☐Yes ☐No

How many times? .

---

12. In the last week have you had any home help?

☐Yes ☐No

How many times? .

---

13. In the last week have you attended a day centre?

☐Yes ☐No

How many times? .

---

14. In the last week have you attended a day hospital?

☐Yes ☐No

How many times? .

---

15. In the last week have you had a district nurse visit you?

☐Yes ☐No

How many times? .

---

16. In the last year, have you been admitted to a respite home for a short time to give yourself and your carer a rest?

☐Yes ☐No

17a. Have you had any physiotherapy in the last year?

☐Yes ☐No→Go to question 18

17b. Have you had this therapy in the last month?

☐Yes ☐No→Go to question 18

17c.Where was the therapy received?

☐Private ☐Acute stroke unit ☐Generic rehab unit

☐Geriatric ☐Acute Medical ☐Community rehab centre

☐ITU/HDU ☐Neurosurgery ☐Rehab at home team

☐Surgery ☐Rehab stroke unit ☐Other-

Specify: Click here to enter text.

18a. Have you had any occupational therapy in the last year?

☐Yes ☐No→Go to question 19

18b. Do you still have this therapy?

☐Yes ☐No→Go to question 19

18c.Where was the therapy received?

☐Private ☐Acute stroke unit ☐Generic rehab unit

☐Geriatric ☐Acute Medical ☐Community rehab centre

☐ITU/HDU ☐Neurosurgery ☐Rehab at home team

☐Surgery ☐Rehab stroke unit ☐Other-

Specify: Click here to enter text.

19a. Have you had any speech or language therapy in the last year?

☐Yes ☐No→Go to question 20

19b. Do you still have this therapy?

☐Yes ☐No→Go to question 20

19c. Where was the therapy received?

☐Private ☐Acute stroke unit ☐Generic rehab unit

☐Geriatric ☐Acute Medical ☐Community rehab centre

☐ITU/HDU ☐Neurosurgery ☐Rehab at home team

☐Surgery ☐Rehab stroke unit ☐Other-

Specify: Click here to enter text.

20a. Have you seen a GP in the last year?

☐Yes ☐No→Go to question 21

20b. Have you seen them in the last month?

☐Yes ☐No

How many times? .

21a. Have you seen a specialist hospital doctor in the last year?

☐Yes ☐No→Go to question 22

21b. Have you seen them in the last month?

☐Yes ☐No

How many times? .

22a. Have you seen a specialist nurse in the community in the last year?

☐Yes ☐No→Go to question 23

22b. Have you seen them in the last month?

☐Yes ☐No

How many times? .

23a. Has your blood pressure been checked in the last year?

☐Yes ☐No→Go to question 24

23b. When was your blood pressure checked?

☐Today ☐In the past week ☐1week-1month ago

☐1-6months ago ☐6-12months ago

23c. What was the most recent blood pressure?

Systolic 4 . Diastolic . ☐I don't remember

(smaller number) (bigger number)

24. Do you currently have weakness or paralysis of a complete body side or an arm or a leg?

☐Yes ☐No ☐I don't know

---

25. Do you currently have slurred speech or problems talking to somebody because your mouth was unable to articulate words or sentences correctly?

☐Yes ☐No ☐I don't know

---

26. Do you currently have any trouble swallowing?

☐Yes ☐No ☐I don't know

---

27. Have you been diagnosed with any of the following in the last year?

Depression ☐Yes ☐No ☐I don't know

Hypertension ☐Yes ☐No ☐I don't know

High Cholesterol ☐Yes ☐No ☐I don't know

Diabetes ☐Yes ☐No ☐I don't know

Atrial fibrillation ☐Yes ☐No ☐I don't know

(Irregular heartbeat)

Angina ☐Yes ☐No ☐I don't know

Peripheral

vascular disease ☐Yes ☐No ☐I don't know

(narrowing of arteries in legs)

Epilepsy ☐Yes ☐No ☐I don't know

Myocardial

infarction ☐Yes ☐No ☐I don't know

(heart attack) ↓

Was it within the last month? ☐Yes ☐No

28. Have tried any of the following in the last year?

Cutting down on salt ☐Yes ☐No ☐ Don't Need to

Cutting down on fatty foods ☐Yes ☐No ☐ Don't Need to

Eating less to lose weight ☐Yes ☐No ☐ Don't Need to

Exercising to lose weight ☐Yes ☐No ☐ Don't Need to

Exercising to get fitter ☐Yes ☐No ☐ Don't Need to

29a.Do you smoke?

☐Yes ☐No→Go to question 29d

29b. If you are a smoker, how much do you smoke a day?

Cigarettes (number)

Tobacco (grams) .

Cigars (number) .

29c.If you are a smoker, have you tried to cut down in the last year?

☐Yes ☐No

29d.If you are a non smoker now, are you an ex-smoker?

☐Yes ☐No→Go to question 30

29e.If you are an ex-smoker, have you given up in the last year?

☐Yes ☐No

30a. Do you drink any alcohol?

☐Yes ☐No→Go to question 31

30b. How much do you drink a week?

Beer (pints) .

Wine (glasses) ☐I don't drink every week

Spirits .

30c Have you cut down on the amount of alcohol you drink in the last year?

☐Yes ☐No ☐Tried but didn't

---

31. Do you feel that you have made a complete recovery from the stroke?

☐Yes ☐No

32. Have you had any written information about preventing further strokes?

☐Yes ☐No ☐I don't know

33. Have you had any advice from your GP about preventing strokes?

☐Yes ☐No ☐I don't know

34a. Are you currently on any medication, including aspirin?

☐Yes ☐No→Go to question 35

34b. Please list all the medications you are currently taking in the spaces provided below

Name of Drug	Dose	How often do you take the drug? (Select from drop-down options)

Please answer yes or no to the following questions about support you receive from those around you

Is anyone helping you to complete the questions in this section?

☐No, I am answering on my own

☐Yes, my carer/family/friend is helping me

☐I am a carer/family/friend answering on his/her behalf

---

1. If you needed help, do you have anyone (e.g. friends, neighbours, family) that you can turn to?

☐Yes ☐No

---

2. Do you have somebody (e.g. friends, neighbours, family) who shows that they care about you?

☐Yes ☐No ☐I don't have any

---

3. Do you see as much of your neighbours as you would like?

☐Yes ☐No ☐I don't have any

---

4. Do you see as much of your relatives as you would like?

☐Yes ☐No ☐I don't have any

---

5. Do you see as much of your friends as you would like?

☐Yes ☐No ☐I don't have any

On the following two pages are some questions about your ability to look after yourself. They may not all seem to apply to you but please answer them all by selecting *one* option which you feel best describes your situation.

Is anyone helping you to complete the questions in this section?

☐No, I am answering on my own

☐Yes, my carer/family/friend is helping me

☐I am a carer/family/friend answering on his/her behalf

---

1. In the bath or shower, do you:

☐manage on your own?

☐need help getting in and out?

☐need other help?

☐need to be washed in bed?

☐never have a bath or shower?

---

2. Can you climb stairs at home:

☐without anyone's help?

☐with someone encouraging you?

☐with someone carrying your frame?

☐with physical help?

☐not at all?

☐don't have stairs?

---

3. Do you get dressed:

☐without any help?

☐just with help with buttons?

☐with someone helping you most of the time?

---

4. Do you walk indoors:

☐without anyone’s help or with a frame?

☐with one person watching over you?

☐with one person helping you

☐with more than one person helping you?

☐not at all?

☐or do you use a wheelchair independently(e.g. round corners)

5. Do you move from bed to chair:

☐on your own?

☐with a little help from one person?

☐with a lot of help from one or more people?

☐not at all?

---

6. Do you eat food:

☐without any help?

☐with some help(such as cutting food or spreading butter)?

☐with more help?

---

7. Do you use the toilet or commode:

☐without anyone's help?

☐with some help but can do some things?

☐with quite a lot of help?

---

8. Do you brush your hair and teeth, wash your face and shave:

☐without help?

☐with help?

---

9. Do you lose control of your bladder? (are you incontinent of urine?):

☐never

☐less than once a week

☐less than once a day

☐more often

☐or do you have a catheter managed for you?

---

10. Do you lose control of your bowel movements? (Do you soil yourself?):

☐never

☐occasional accident

☐all the time

We are interested in finding out how often you carry out some activities. As you will see, the first page is about activities during the last *3 months* and over the page asks about the last *6 months*.

Please remember to select one box only for each question.

Is anyone helping you to complete the questions in this section?

☐No, I am answering on my own

☐Yes, my carer/family/friend are helping me

☐I am a carer/family/friend answering on his/her behalf

In the last 3 months how often have you carried out these activities?

1. Preparing main meals (not just a snack)

☐Never ☐ Less than once a week ☐1 or 2 times a week ☐Most days

---

2. Washing up (Do all after one meal or share equally with another person)

☐Never ☐ Less than once a week ☐1 or 2 times a week ☐Most days

---

Over the last 3 months how often have you carried out these activities?

3. Washing clothes (e.g. loading and unloading washing machine)

☐Never ☐Only once or twice ☐1 to 4 times a month ☐At least once a week

---

4. Light housework (e.g. dusting, or tidying small objects)

☐Never ☐Only once or twice ☐1 to 4 times a month ☐At least once a week

---

5. Heavy housework (e.g. hoovering, or making beds)

☐Never ☐Only once or twice ☐1 to 4 times a month ☐At least once a week

---

6. Local shopping

☐Never ☐Only once or twice ☐1 to 4 times a month ☐At least once a week

---

7. Social occasions (including going to church)

☐Never ☐Only once or twice ☐1 to 4 times a month ☐At least once a week

---

8. Walking outside for over 15 minutes

☐Never ☐Only once or twice ☐1 to 4 times a month ☐At least once a week

---

9. Taking part in a hobby activity

☐Never ☐Only once or twice ☐1 to 4 times a month ☐At least once a week

---

10. Going on a bus or driving a car

☐Never ☐Only once or twice ☐1 to 4 times a month ☐At least once a week

---

In the last <u>6 months</u> how often have you carried out the following activities?

11. Travel outings or car rides (travel for pleasure, not just for routine trips)

☐Never ☐Only once or twice ☐1 to 2 times a month ☐At least once a week

---

12.Gardening

☐Never ☐Light (e.g. occasional weeding) ☐Moderate

☐All necessary (Includes heavy digging)

---

13. Household or car maintenance

☐Never ☐Light (e.g. small repairs) ☐Moderate (painting) ☐All necessary

---

14. Reading books (not just magazines)

☐Never ☐One in 6 months ☐Less than 1 a fortnight ☐More than 1 a fortnight

---

15. Paid work

☐None ☐Up to 10hrs a week ☐10-30hrs a week ☐More than 30hrs a week

---

The following questions ask for your views about your health, how you feel and how well you are able to do your usual activities.

If you are unsure about how to answer any questions please give the best answer you can. Do not spend too much time in answering as your immediate response is likely to be the most accurate.

Is anyone helping you to complete the questions in this section?

☐No, I am answering on my own

☐Yes, my carer/family/friend are helping me

☐I am a carer/family/friend answering on his/her behalf.

---

1. In general, would you say your health is:

☐Excellent ☐Very Good ☐Good ☐Fair ☐Poor

---

2. Health and daily activities. The following questions are about activities you might do during a particular day. Does your health limit you in these activities? If so, how much?

A. Moderate activities (such as moving a table, pushing a vacuum, bowling or playing golf)

☐Yes, limited a lot

☐Yes, limited a little

☐No, not limited at all

B. Climbing several flights of stairs

☐Yes, limited a lot

☐Yes, limited a little

☐No, not limited at all

---

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Please answer Yes or No to each question)

A. Accomplished less than you would like

☐Yes ☐No

B. Were limited in the kind of work or other activities

☐Yes ☐No

---

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Please answer Yes or No to each question)

A. Accomplished less than you would like

☐Yes ☐No

B. Didn't do work or activities as carefully as usual

☐Yes ☐No

5. During the past 4 weeks how much did pain interfere with your normal work (including work both outside the home and housework)? (Please tick one box)

☐Not at all ☐A little bit ☐Quite a bit ☐Moderately ☐Extremely

---

6. These questions are about how you feel and how things have been with you during the past month. For each question, please indicate the one answer that comes closest to the way you have been feeling. (Please tick one box)

How much time during the last month:

A. Have you felt calm and peaceful?

☐All of the time

☐Most of the time

☐A good bit of the time

☐Some of the time

☐A little of the time

☐None of the time

B. Did you have a lot of energy?

☐All of the time

☐Most of the time

☐A good bit of the time

☐Some of the time

☐A little of the time

☐None of the time

C. Have you felt downhearted and low?

☐All of the time

☐Most of the time

☐A good bit of the time

☐Some of the time

☐A little of the time

☐None of the time

D. Has your health limited your social activities?

☐All of the time

☐Most of the time

☐A good bit of the time

☐Some of the time

☐A little of the time

☐None of the time

This questionnaire is designed to help us know how you feel. Please give the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

Is anyone helping you to complete the questions in this section?

☐No, I am answering on my own

☐Yes, my carer/family/friend are helping me

☐I am a carer/family/friend answering on his/her behalf

---

1. I feel tense or 'wound up':

☐most of the time ☐a lot of the time ☐occasionally ☐ not at all

---

2. I feel as if I am slowed down:

☐nearly all the time ☐very often ☐sometimes ☐not at all

---

3. I still enjoy the things I used to:

☐definitely as much ☐not quite as much ☐only a little ☐hardly at all

4. I get a sort of frightened feeling like butterflies in my stomach:

☐not at all ☐occasionally ☐quite often ☐very often

5. I get a sort of frightened feeling as if something awful is about to happen:

☐very definitely and quite badly ☐yes, but not too badly

☐a little, but it doesn't worry me ☐not at all

6. I have lost interest in my appearance:

☐definitely ☐I don't take as much care as I should

☐I may not take as much care as I should

☐I take just as much care as ever

7. I can laugh and see the funny side of things:

☐as much as I always could ☐definitely not so much now

☐not quite so much now ☐not at all

8. I feel restless as if I have to be on the move:

☐very much indeed ☐quite a lot ☐not very much ☐not at all

9. Worrying thoughts go through my mind:

☐a great deal of the time ☐a lot of the time

☐from time to time ☐only occasionally

10. I look forward with enjoyment to things:

☐as much as I ever did ☐definitely less than I used to

☐rather less than I used to ☐hardly at all

11. I feel cheerful:

☐not at all ☐not often

☐sometimes ☐most of the time

12. I get sudden feelings of panic:

☐very often indeed ☐quite often

☐not very often ☐not at all

---

13. I can sit at ease and feel relaxed:

☐definitely ☐usually ☐not often ☐not at all

---

14. I can enjoy a good book or radio or TV programme:

☐often ☐sometimes ☐not often ☐very seldom

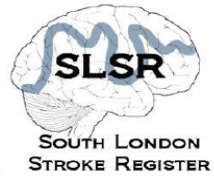
(iv) SLSR CONSENT FORM

St George's Healthcare NHS

Guy's and St Thomas' NHS
NHS Foundation Trust

The Lewisham Hospital NHS
NHS Trust

King's College Hospital NHS
NHS Foundation Trust



CONSENT FORM
South London Stroke Register

1. I have read and understand the information booklet date 20/02/2012 (version 2) about the South London Stroke Register and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I understand that members of the research team will have access to my medical notes.

4. I agree to the researchers contacting my doctor or myself in future to obtain follow up information.

5. I agree to take part in the above research.

Name of patient _____

Signature _____ Date _____

Name of person taking consent _____

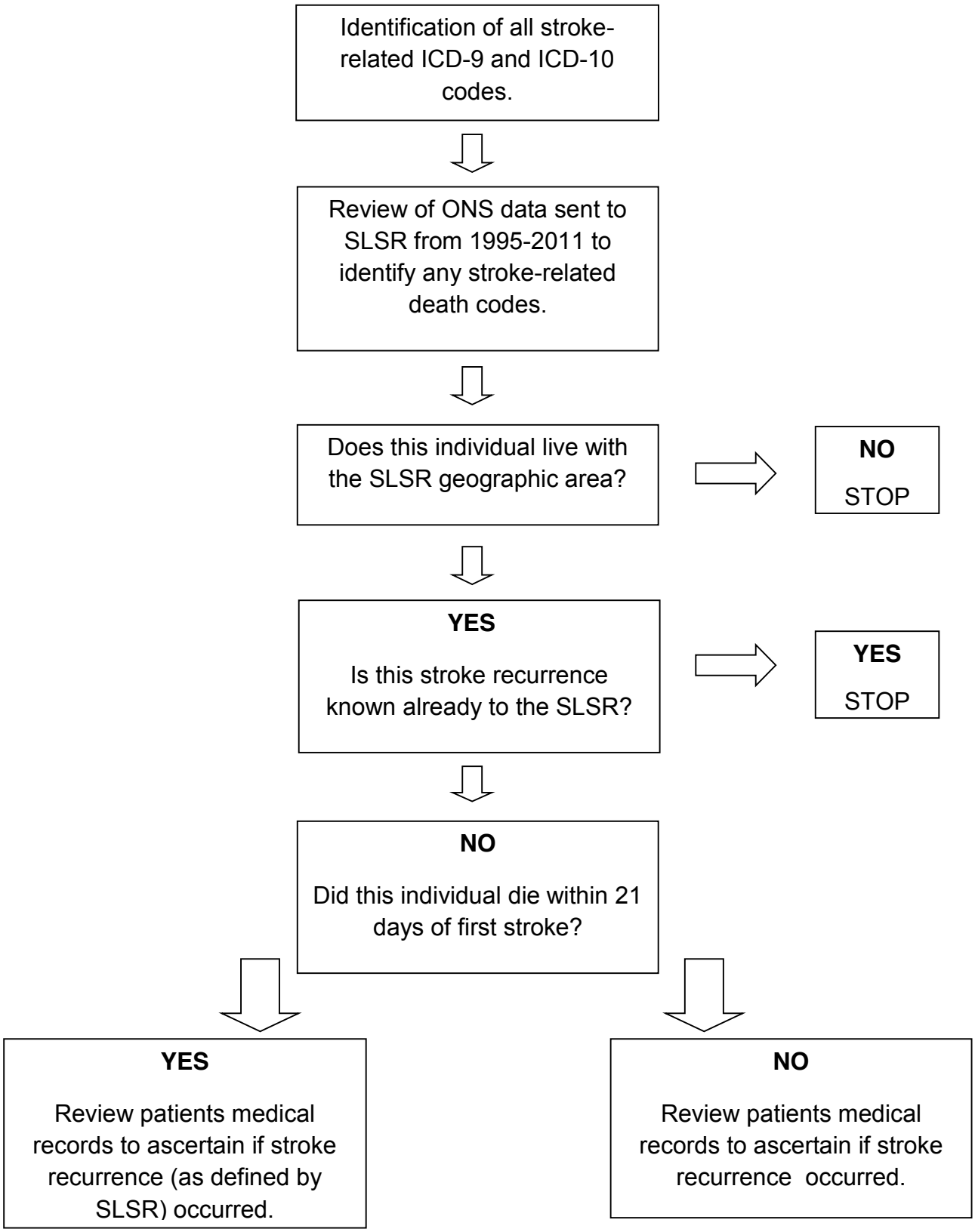
Signature _____ Date _____

Ethics Committee reference number: 01-195

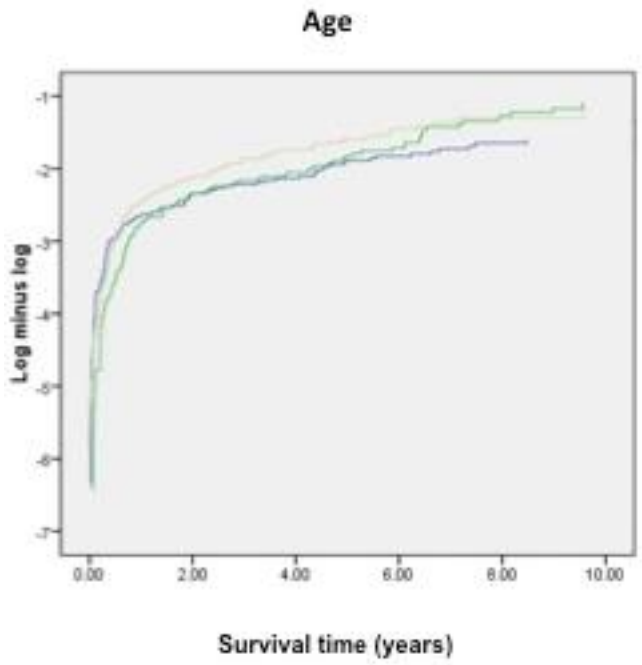
Date of approval: 23/01/2008

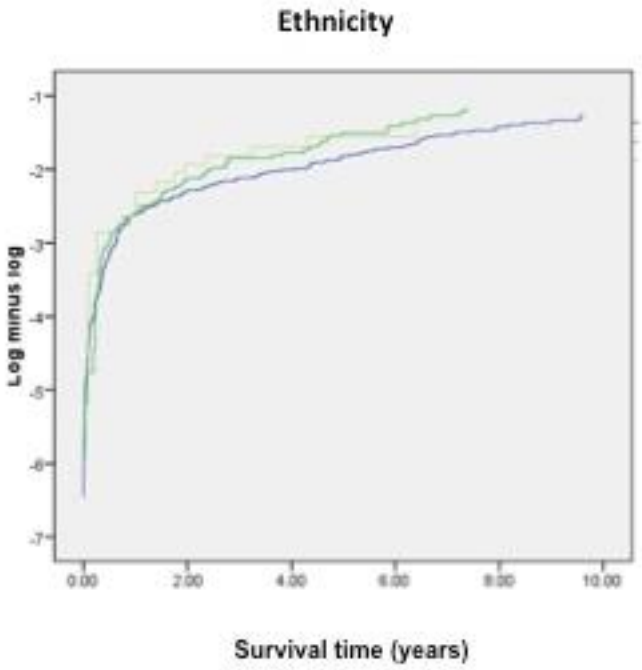
Version 2

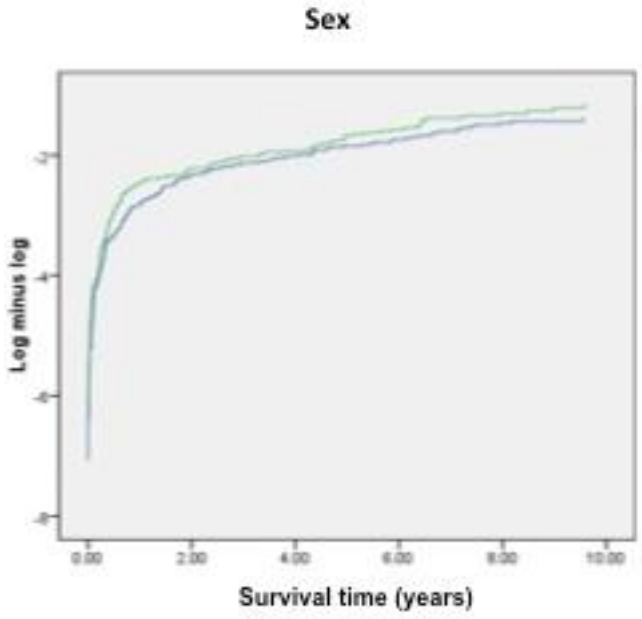
Appendix 3. Algorithm for identifying patients with stroke recurrence using routine death data from the Office for National Statistics (ONS).

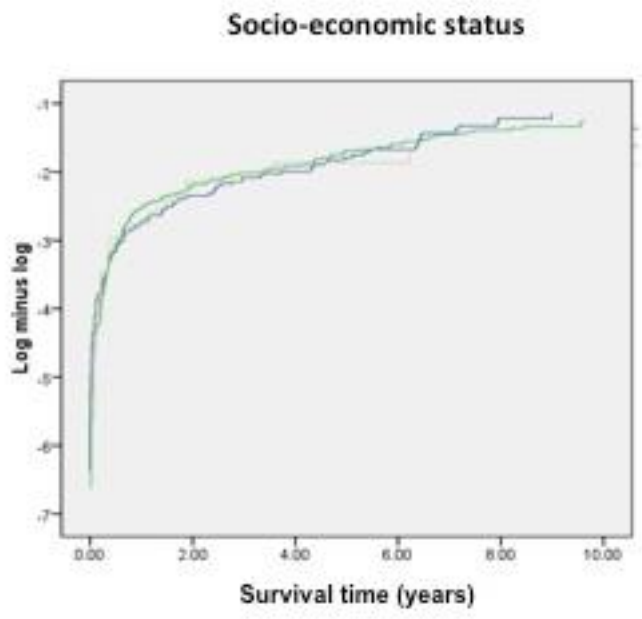


Appendix 4. : Log-log plots showing proportional hazards assumption filled across all variables in the model used in Chapter 3

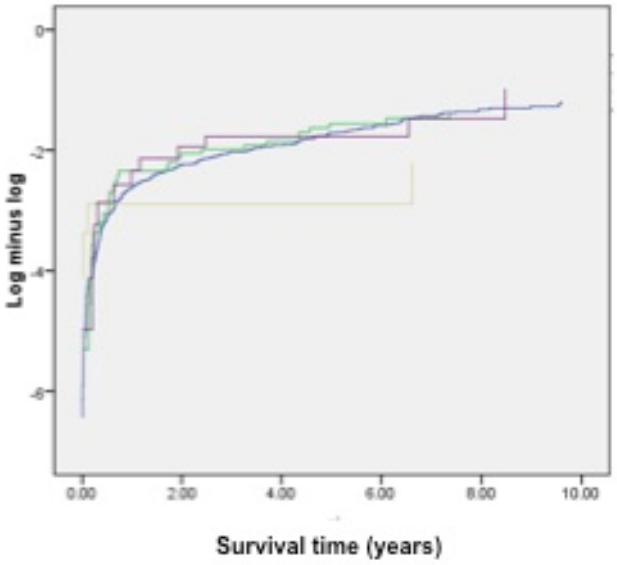




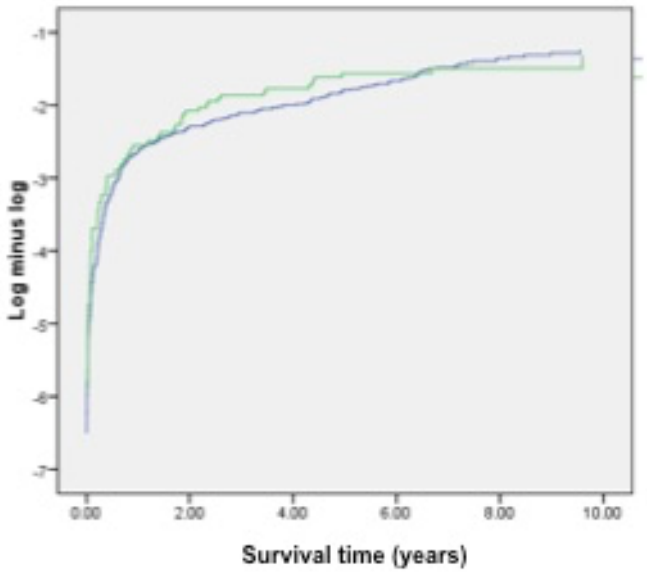




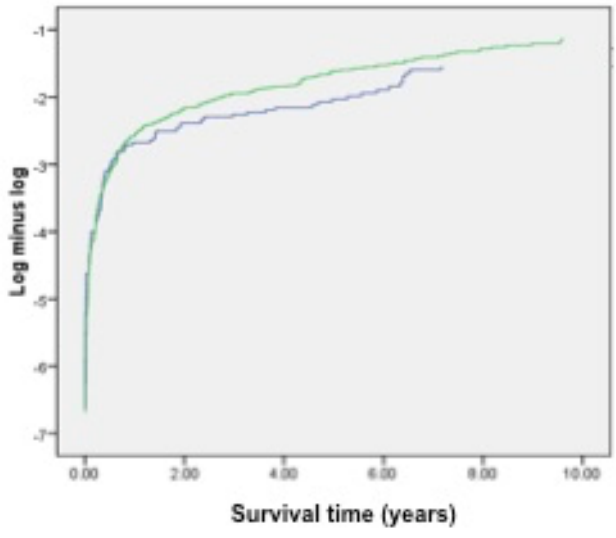
Stroke subtype



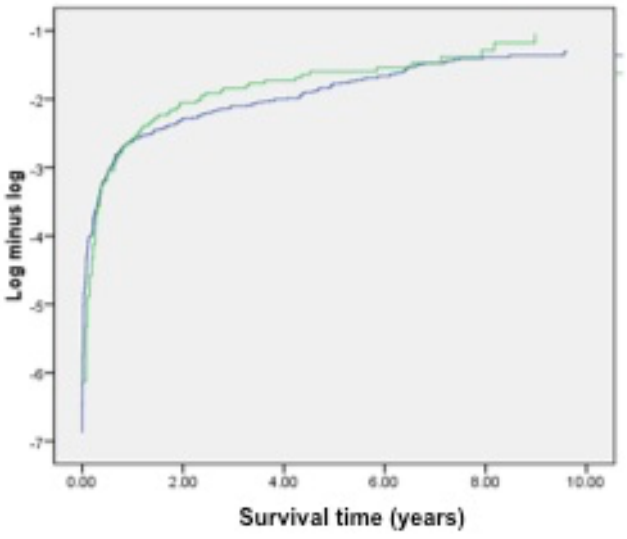
Past history of TIA



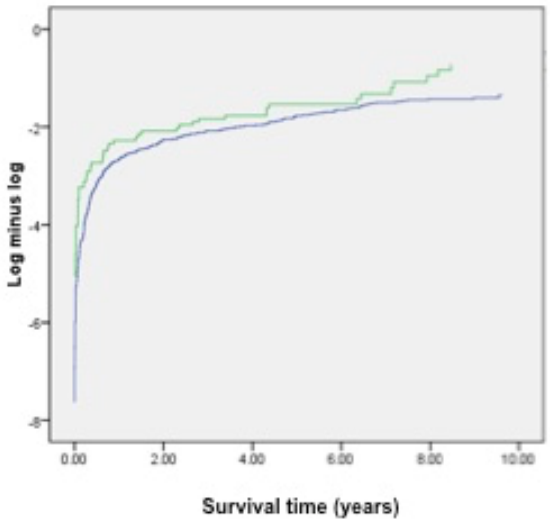
Past history of hypertension



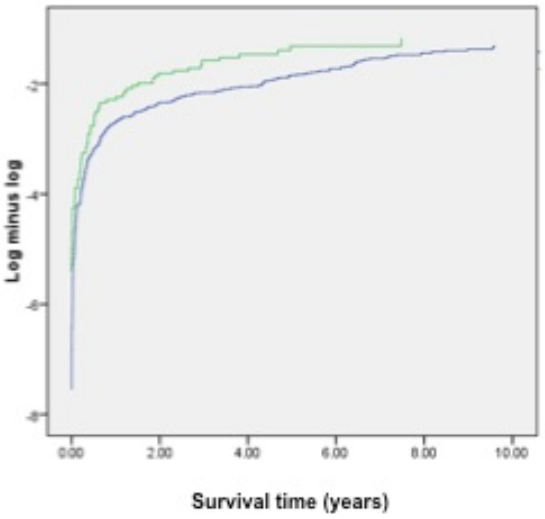
Past history of Diabetes Mellitis



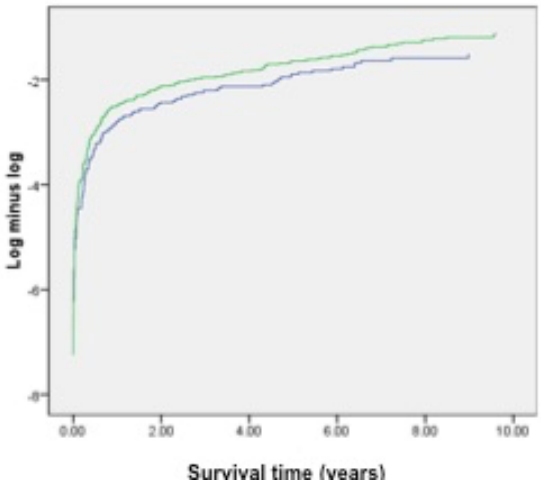
Past history of MI



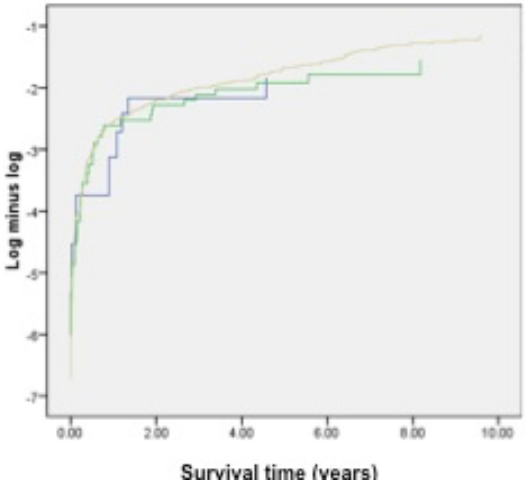
Past history of AF



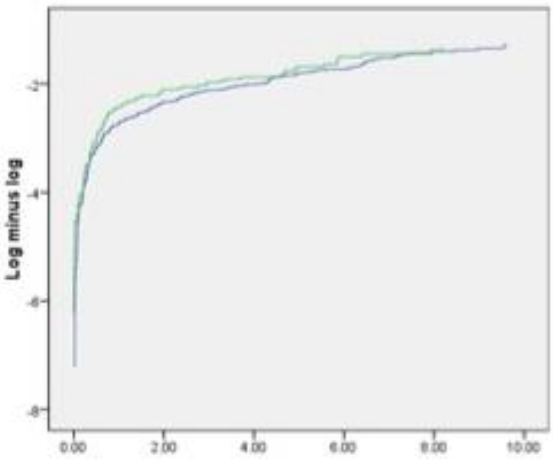
Smoking status



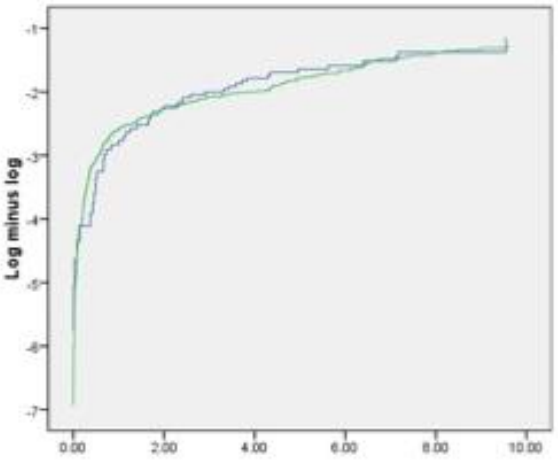
GCS on admission



Incontinence on admission



Motor deficit on admission



Appendix 5. Medication within each category of secondary prevention for analyses in Chapter 6

Secondary prevention treatment variable	Medication generic/trade name
Anti-hypertensive medications	CANDESARTAN CAPTOPRIL CILAZAPRIL COZAAR ENALAPRIL FOSINOPRIL INNOVACE LISINOPRIL LOSARTAN OLMESARTAN PERINDOPRIL QUINAPRIL RAMIPRIL RASILEZ STARIL TRANDOLAPRIL TRITACE ZESTORETIC ADALAT CAPOTEN CARDURA CARVEDILOL CLONIDINE COTENIDINE DECLINAX DILTIAZEM DOXAZOSIN DRONEDARONE EPROSARTAN FELODIPINE HYDRALAZINE IRBESARTAN ISRADIPINE ISTIN LACIDIPINE LERCANIDIPINE METHYLDOPA MINOXIDIL MONOXIDINE

	NAVISPARE NEBIVOLOL NIFEDIPINE PRAZOSIN SECURON TELMISARTAN TERAZOSIN TILDIEM VALSARTAN VERAPAMIL AMLODIPINE PROPANOLOL ACEBUTOLOL ATENOLOL BISOPROLOL COTENIDONE LABETALOL METOPROLOL SLOW TRASICOR TENIF TENORETIC TENORMIN AMILORIDE APRINOX BENDROFLUAZIDE BENDROFLUMETHAZIDE BENDROFLUMEZIDE BUMETANIDE CHLORTHALIDONE CO AMILOFRUSE CO-AMILOZIDE EPLERENONE FRUMIL FRUSEMIDE FUROSEMIDE HYDROCHLOROTHIAZIDE HYGROTEN K INDAPAMIDE METOLAZONE NATRILIX SPIRONOLACTONE THIAZIDE
Anticoagulant medications	ACENOCOUMAROL ANTICOAGULANT APIXABAN DABIGATRAN

	DALTEPARIN ENOXAPARIN FONDAPARINUX HEPARIN RIVAROXABAN WARFARIN
Lipid-lowering medications	BEZAFIBRATE BEZALIP FENOFIBRATE COLESTYRAMINE EZETIMIBE OMACOR ATORVASTATIN CRESTOR FLUVASTATIN INEGY LIPITOR PRAVASTATIN ROSUVASTATIN SIMVASTATIN ZOCOR
Antiplatelet medications	ASASANTIN CLOPIDOGREL DIPYRIDAMOLE PERSANTIN PLAVIX PRASUGREL TERUTROBAN TICLOPIDINE

APPENDIX 6: Number of cases remaining in studies undertaken as part of this thesis during follow-up period, by covariate

(1) Dataset used for analyses in Chapter 3

(i) 0-1 years after first stroke

(ii) 1-5 years after first stroke

(iii) 5-10 years after first stroke

(2) Dataset used for analyses in Chapters 5 & 6

(i) 0-1 years after first stroke – all strokes

(ii) 1-5 years after first stroke – all strokes

(iii) 5-12 years after first stroke – all strokes

(iv) 0-1 years after first stroke – ischaemic strokes only

(v) 1-5 years after first stroke – ischaemic strokes only

(vi) 5-12 years after first stroke – ischaemic strokes only

(3) Dataset used for analyses in Chapter 7

(i) 0-1 years after first stroke

(ii) 1-5 years after first stroke

(iii) 5-10 years after first stroke

(iv) 10-15 years after first stroke

(1) Dataset used for analyses in Chapter 3

(i) 0-1 years after first stroke

	Number with stroke recurrence	Number censored - died	Number censored – end of time period	Number in study– at end of time-period –
Total	142 (4.9%)	1042 (36.2)	65 (2.3)	1625 (56.6%)
Age group				
<65	42	189	37	595
65-74	37	217	21	489
>75	63	636	7	541
Age group unknown	0	0	0	0
Gender				
Male	62	439	41	885
Female	80	603	24	740
Gender unknown	0	0	0	0
Ethnicity				
White	107	848	33	1138
Black	25	122	15	363
Other	9	9	13	99
Ethnicity unknown	1	1	4	25
Socio economic status				
Non-manual	37	201	17	475
Manual	92	492	33	987
Unknown	13	349	15	163
Stroke Subtype				
Infarct	111	629	47	1302
PICH	16	192	8	179
SAH	5	77	8	81
Stroke subtype unknown	10	144	2	63
Baseline Risk factors				

No TIA	113	819	57	1326
Previous TIA	26	122	4	206
Previous TIA unknown	3	101	4	93
No Hypertension	44	357	33	526
Hypertension	95	591	27	1001
Hypertension unknown	3	94	5	98
No Diabetes Mellitus	110	798	49	1248
Diabetes Mellitus	29	166	7	281
Diabetes unknown	3	78	9	96
No MI	116	816	58	1385
Previous MI	24	142	2	147
Previous MI unknown	2	84	5	93
No AF	112	705	58	1350
Previous AF	27	250	3	183
AF unknown	3	87	4	92
Non-Smoker	45	358	30	560
Smoker or ex-smoker	54	233	8	419
Smoking status unknown	43	451	27	646
Stroke severity Indices				
GCS ≤8	4	421	0	72
9-12	19	223	6	174
13-15	114	342	56	1323
GCS unknown	5	56	3	56
No motor deficit	23	61	16	322
Motor deficit	118	837	47	1280
Motor deficit unknown	1	144	2	23
No incontinence	80	171	49	1082
Incontinence	52	723	10	454
Incontinence unknown	10	148	6	89

(ii) 1 to 5 years

	Number with stroke recurrence	Number censored - died	Number censored – end of time period	Number in study– at end of time-period –
Total	122 (7.5%)	440 (27.1%)	345 (21.2%)	122 (7.5%)
Age group				
<65	32	74	163	326
65-74	40	135	91	223
>75	50	231	91	119
Age group unknown	0	0	0	0
Gender				
Male	71	212	194	408
Female	51	228	151	310
Gender unknown	0	0	0	0
Ethnicity				
White	81	349	209	499
Black	32	65	99	167
Other	7	18	31	43
Ethnicity unknown	2	8	6	9
Socio economic status				
Non-manual	33	116	108	218
Manual	79	289	194	425
Unknown	10	35	43	75
Stroke Subtype				
Infarct	103	380	272	547
PICH	13	39	37	90
SAH	0	5	5	50
Stroke subtype unknown	6	16	16	31
Baseline Risk factors				
No TIA	90	357	304	575
Previous TIA	23	60	32	91
Previous TIA unknown	9	23	9	52

No Hypertension	26	130	126	244
Hypertension	88	283	208	422
Hypertension unknown	8	27	11	52
No Diabetes Mellitus	86	331	272	559
Diabetes Mellitus	29	84	58	110
Diabetes unknown	7	25	15	49
No MI	99	375	308	603
Previous MI	14	41	29	63
Previous MI unknown	9	25	8	52
No AF	94	345	298	613
Previous AF	21	70	37	55
AF unknown	7	25	10	50
Non-Smoker	42	154	124	240
Smoker or ex-smoker	33	129	93	164
Smoking status unknown	47	157	128	314
Stroke severity Indices				
GCS ≤8	4	18	19	31
9-12	9	50	36	79
13-15	100	358	277	588
GCS unknown	9	14	13	20
No motor deficit	28	58	72	164
Motor deficit	92	374	267	547
Motor deficit unknown	2	8	6	7
No incontinence	84	245	236	517
Incontinence	26	169	84	175
Incontinence unknown	12	26	25	26

(iii) 5 to 10 years

	Number with stroke recurrence	Number censored - died	Number censored – end of time period	Number in study– at end of time-period –
Total	39 (5.4%)	203 (28.3%)	391 (54.4%)	85 (11.8%)
Age group				
<65	11	45	219	51
65-74	20	71	106	26
>75	8	87	66	8
Age group unknown	0	0	0	0
Gender				
Male	21	116	219	52
Female	18	87	172	33
Gender unknown	0	0	0	0
Ethnicity				
White	28	165	250	56
Black	9	25	108	25
Other	2	10	27	4
Ethnicity unknown	0	3	6	0
Socio economic status				
Non-manual	16	55	121	26
Manual	21	129	220	55
Unknown	2	19	50	4
Stroke Subtype				
Infarct	32	163	292	60
PICH	2	29	45	14
SAH	1	2	39	8
Stroke subtype unknown	4	9	15	3
Baseline Risk factors				
No TIA	36	150	322	67
Previous TIA	2	41	33	15
Previous TIA unknown	1	12	36	3

No Hypertension	11	58	148	27
Hypertension	26	133	208	35
Hypertension unknown	2	12	35	3
No Diabetes Mellitus	31	153	301	74
Diabetes Mellitus	6	38	58	8
Diabetes unknown	2	12	32	3
No MI	31	160	336	76
Previous MI	7	29	21	6
Previous MI unknown	1	14	34	3
No AF	37	162	337	77
Previous AF	1	28	21	5
AF unknown	1	13	13	3
Non-Smoker	10	60	144	26
Smoker or ex-smoker	10	59	75	20
Smoking status unknown	19	84	172	39
Stroke severity Indices				
GCS ≤8	0	6	17	8
9-12	2	23	44	10
13-15	35	168	321	64
GCS unknown	2	6	9	3
No motor deficit	5	33	107	19
Motor deficit	33	170	278	66
Motor deficit unknown	1	0	6	0
No incontinence	30	138	293	56
Incontinence	7	56	87	25
Incontinence unknown	2	9	11	4

2) Dataset used for analyses in Chapters 5 & 6

(i) 0-1 years after first stroke – all strokes

	Number with stroke recurrence	Number censored - died	Number censored – at last follow-up	Number in study– at end of time-period –
Total	191 (4.8%)	687 (17.1%)	891 (22.2%)	2253 (56.0%)
Age group				
<65	56	128	218	846
65-74	49	136	200	655
>75	86	423	473	752
Age group unknown	0	0	0	0
Gender				
Male	86	304	397	1236
Female	105	382	488	1015
Gender unknown	0	1	6	2
Ethnicity				
White	138	549	671	1531
Black	40	85	145	535
Other	12	27	41	145
Ethnicity unknown	1	26	34	42
Socio economic status				
Non-manual	53	134	221	674
Manual	120	300	402	1325
Unknown	9	56	63	103
Economically inactive	9	197	205	151
Baseline Risk factors				
No TIA	151	548	745	1886
Previous TIA	36	68	100	268
Previous TIA unknown	4	71	46	99
No MI	160	546	742	1956

Previous MI	29	79	109	197
Previous MI unknown	2	62	40	100
No Diabetes Mellitus	149	540	688	1734
Diabetes Mellitus	37	90	168	416
Diabetes unknown	5	57	35	103
Time-dependent risk factors				
No hypertension	64	224	346	737
Hypertension – no treatment	46	136	190	482
Hypertension –on treatment	75	242	301	884
Hypertension – unknown treatment	3	20	13	43
Unknown hypertension	3	65	41	107
No hypercholesterolaemia	90	336	495	1213
Hypercholesterolaemia, no treatment	4	16	30	78
Hypercholesterolaemia, on treatment	14	37	100	232
Hypercholesterolaemia, unknown treatment	3	3	1	16
Unknown hypercholesterolaemia	80	294	265	714
No antiplatelet medication	138	431	567	1464
On antiplatelet medication	45	164	259	613
Unknown antiplatelet medication	8	92	65	176
No AF	148	457	670	1913
AF diagnosed, no treatment	27	142	141	195
AF diagnosed, on treatment	7	21	31	40
AF diagnosed, unknown treatment	3	6	3	6
Unknown AF	6	61	46	99

(ii) 1-5 years after first stroke – all strokes

	Number with stroke recurrence	Number censored - died	Number censored – at last follow-up	Number in study– at end of time-period –
Total	149 (6.6%)	290 (12.9%)	824 (36.6%)	990 (43.9%)
Age group				
<65	44	44	300	458
65-74	46	80	231	298
>75	59	166	293	234
Age group unknown	0	0	0	0
Gender				
Male	89	153	438	556
Female	60	136	385	434
Gender unknown	0	1	1	0
Ethnicity				
White	95	228	554	654
Black	42	44	201	248
Other	8	12	50	75
Ethnicity unknown	4	6	19	13
Socio economic status				
Non-manual	40	84	246	304
Manual	96	176	463	590
Unknown	3	8	43	46
Economically inactive	10	22	72	47
				3
Baseline Risk factors				
No TIA	115	231	722	818
Previous TIA	24	48	81	115
Previous TIA unknown	10	11	21	57
No MI	124	249	735	848
Previous MI	15	29	67	86
Previous MI unknown	10	12	22	56

No Diabetes Mellitus	108	226	628	772
Diabetes Mellitus	33	50	175	158
Diabetes unknown	8	14	21	60
Time-dependent risk factors				
No hypertension	35	77	286	339
Hypertension – no treatment	34	70	165	213
Hypertension –on treatment	69	121	337	357
Hypertension – unknown treatment	2	9	9	23
Unknown hypertension	9	13	27	58
No hypercholesterolaemia	78	131	520	484
Hypercholesterolaemia, no treatment	4	3	34	37
Hypercholesterolaemia, on treatment	8	32	134	58
Hypercholesterolaemia, unknown treatment	2	1	7	6
Unknown hypercholesterolaemia	57	123	129	405
No antiplatelet medication	93	170	529	672
On antiplatelet medication	44	95	254	220
Unknown antiplatelet medication	12	25	41	98
No AF	120	223	715	855
AF diagnosed, no treatment	18	44	74	59
AF diagnosed, on treatment	3	9	11	17
AF diagnosed, unknown treatment	0	2	2	2
Unknown AF	8	12	22	57

(iii) 5-12 years after first stroke – all strokes

	Number with stroke recurrence	Number censored - died	Number censored – at last follow-up	Number in study– at end of time-period –
Total	53 (5.4%)	165 (16.7%)	660 (66.7%)	112 (11.3%)
Age group				
<65	13	34	340	71
65-74	28	54	183	33
>75	12	77	137	8
Age group unknown	0	0	0	0
Gender				
Male	30	83	378	65
Female	23	82	282	47
Gender unknown	0	0	0	0
Ethnicity				
White	36	129	409	80
Black	14	24	182	28
Other	3	12	57	3
Ethnicity unknown	0	0	12	1
Socio economic status				
Non-manual	21	49	199	35
Manual	29	103	387	71
Unknown	4	2	42	4
Economically inactive	2	11	32	2
Baseline Risk factors				
No TIA	47	127	550	94
Previous TIA	5	29	67	14
Previous TIA unknown	1	9	43	4
No MI	45	129	572	102
Previous MI	7	27	46	6
Previous MI unknown	1	9	42	4

No Diabetes Mellitus	42	124	509	97
Diabetes Mellitus	9	32	106	11
Diabetes unknown	2	9	45	4
Time-dependent risk factors				
No hypertension	15	56	228	40
Hypertension – no treatment	21	37	119	36
Hypertension –on treatment	14	57	255	31
Hypertension – unknown treatment	1	6	15	1
Unknown hypertension	2	9	43	4
No hypercholesterolaemia	20	64	396	4
Hypercholesterolaemia, no treatment	1	7	28	1
Hypercholesterolaemia, on treatment	1	5	52	0
Hypercholesterolaemia, unknown treatment	0	0	6	0
Unknown hypercholesterolaemia	31	89	178	107
No antiplatelet medication	31	101	448	92
On antiplatelet medication	16	46	143	15
Unknown antiplatelet medication	6	18	69	5
No AF	50	130	572	103
AF diagnosed, no treatment	1	21	33	4
AF diagnosed, on treatment	1	4	12	0
AF diagnosed, unknown treatment	0	1	1	0
Unknown AF	1	9	42	5

(iv) 0-1 years after first stroke – ischaemic strokes only

	Number with stroke recurrence	Number censored - died	Number censored – at last follow-up	Number in study– at end of time-period –
Total	162 (4.9%)	503 (15.3%)	709 (21.5%)	1919 (58.3%)
Age group				
<65	44	57	139	647
65-74	41	98	157	586
>75	77	348	413	686
Age group unknown	0	0	0	0
Gender				
Male	75	203	301	1058
Female	87	299	402	859
Gender unknown	0	1	6	2
Ethnicity				
White	120	419	552	1337
Black	32	54	105	426
Other	9	10	31	116
Ethnicity unknown	1	20	21	40
Socio economic status				
Non-manual	44	92	178	558
Manual	103	239	330	1148
Unknown	7	23	34	79
Economically inactive	8	149	167	134
Baseline Risk factors				
No TIA	123	397	587	1598
Previous TIA	35	60	91	244
Previous TIA unknown	4	46	31	77
No MI	132	398	587	1655
Previous MI	28	67	95	186
Previous MI unknown	2	38	27	78

No Diabetes Mellitus	125	396	535	1460
Diabetes Mellitus	33	73	154	379
Diabetes unknown	4	34	20	80
Time-dependent risk factors				
No hypertension	54	155	265	609
Hypertension – no treatment	38	99	148	395
Hypertension –on treatment	65	195	260	793
Hypertension – unknown treatment	2	12	11	40
Unknown hypertension	3	42	25	82
No hypercholesterolaemia	69	235	382	1015
Hypercholesterolaemia, no treatment	4	13	26	72
Hypercholesterolaemia, on treatment	13	32	89	219
Hypercholesterolaemia, unknown treatment	2	2	1	15
Unknown hypercholesterolaemia	74	221	211	598
No antiplatelet medication	113	310	429	1213
On antiplatelet medication	41	136	237	559
Unknown antiplatelet medication	8	57	43	147
No AF	125	313	527	1614
AF diagnosed, no treatment	25	129	131	190
AF diagnosed, on treatment	4	16	19	32
AF diagnosed, unknown treatment	2	6	3	6
Unknown AF	6	39	29	77

(v) 1-5 years after first stroke – ischaemic strokes only

	Number with stroke recurrence	Number censored - died	Number censored – at last follow-up	Number in study– at end of time-period –
Total	130 (6.8%)	263 (13.7%)	724 (37.7%)	802 (41.8%)
Age group				
<65	34	38	239	336
65-74	41	72	216	257
>75	55	153	269	209
Age group unknown	0	0	0	0
Gender				
Male	80	140	387	451
Female	50	122	336	351
Gender unknown	0	1	1	0
Ethnicity				
White	87	210	496	544
Black	34	36	169	187
Other	5	11	41	59
Ethnicity unknown	4	6	18	12
Socio economic status				
Non-manual	35	76	214	233
Manual	82	161	408	497
Unknown	3	8	34	34
Economically inactive	10	18	68	38
Baseline Risk factors				
No TIA	98	211	632	657
Previous TIA	22	42	77	103
Previous TIA unknown	10	10	15	42
No MI	105	225	643	682
Previous MI	15	27	66	78
Previous MI unknown	10	11	15	42

No Diabetes Mellitus	92	207	546	615
Diabetes Mellitus	30	43	163	143
Diabetes unknown	8	13	15	44
Time-dependent risk factors				
No hypertension	27	74	243	265
Hypertension – no treatment	28	61	142	164
Hypertension –on treatment	64	109	312	308
Hypertension – unknown treatment	2	7	9	22
Unknown hypertension	9	12	18	43
No hypercholesterolaemia	67	121	444	383
Hypercholesterolaemia, no treatment	4	3	32	33
Hypercholesterolaemia, on treatment	8	28	129	54
Hypercholesterolaemia, unknown treatment	2	1	6	6
Unknown hypercholesterolaemia	49	110	113	326
No antiplatelet medication	80	155	452	526
On antiplatelet medication	38	86	239	196
Unknown antiplatelet medication	12	22	33	80
No AF	101	199	626	688
AF diagnosed, no treatment	18	44	71	57
AF diagnosed, on treatment	3	7	10	12
AF diagnosed, unknown treatment	0	2	2	2
Unknown AF	8	11	15	43

(vi) 5-12 years after first stroke – ischaemic strokes only

	Number with stroke recurrence	Number censored - died	Number censored – at last follow-up	Number in study– at end of time-period –
Total	47 (5.7%)	146 (18.2%)	526 (65.6%)	83 (10.3%)
Age group				
<65	10	29	249	48
65-74	25	46	159	27
>75	12	71	118	8
Age group unknown	0	0	0	0
Gender				
Male	25	76	299	51
Female	22	70	227	32
Gender unknown	0	0	0	0
Ethnicity				
White	32	117	334	61
Black	12	17	139	19
Other	3	12	42	2
Ethnicity unknown	0	0	11	1
Socio economic status				
Non-manual	19	43	149	22
Manual	25	91	325	56
Unknown	1	2	28	3
Economically inactive	2	10	24	2
Baseline Risk factors				
No TIA	42	110	436	69
Previous TIA	4	27	61	11
Previous TIA unknown	1	9	29	3
No MI	39	114	455	74
Previous MI	7	23	42	6
Previous MI unknown	1	9	29	3

No Diabetes Mellitus	36	105	403	71
Diabetes Mellitus	9	32	93	9
Diabetes unknown	2	9	30	3
Time-dependent risk factors				
No hypertension	14	47	176	28
Hypertension – no treatment	17	33	90	24
Hypertension –on treatment	13	51	217	27
Hypertension – unknown treatment	1	6	14	1
Unknown hypertension	2	9	29	3
No hypercholesterolaemia	18	56	306	3
Hypercholesterolaemia, no treatment	1	6	25	1
Hypercholesterolaemia, on treatment	1	5	48	0
Hypercholesterolaemia, unknown treatment	0	0	6	0
Unknown hypercholesterolaemia	27	79	141	79
No antiplatelet medication	27	86	348	65
On antiplatelet medication	14	43	125	14
Unknown antiplatelet medication	6	17	53	4
No AF	44	112	457	75
AF diagnosed, no treatment	1	20	32	4
AF diagnosed, on treatment	1	4	7	0
AF diagnosed, unknown treatment	0	1	1	0
Unknown AF	1	9	29	4

(3) Dataset used for analyses in Chapter 7

(i) 0-1 years after first stroke

	Number died - no recurrence	Number died - with recurrence	Number in study at end of time-period – no recurrence	Number in study at end of time-period – with recurrence
Total	1433 (32.0%)	63 (1.4%)	2858 (63.8)	124 (2.8)
Age group				
<65	244	8	1140	48
65-74	300	17	778	31
>75	889	38	940	45
Age group unknown	0	0	0	0
Gender				
Male	612	23	1572	61
Female	821	40	1286	63
Gender unknown	0	0	0	0
Ethnicity				
White	1124	49	1897	83
Black	190	11	724	31
Other	56	2	189	10
Ethnicity unknown	63	1	48	0
Socio economic status				
Non-manual	283	18	904	35
Manual	609	36	1615	81
Unknown	109	3	174	6
Economically inactive	466	6	253	2
Stroke Subtype				
Infarct	911	50	2295	95
PICH	268	7	289	13
SAH	91	2	124	7

Stroke subtype unknown	164	4	150	9
Year of initial stroke				
1995-1998	496	24	737	48
1999-2002	385	15	638	36
2003-2006	286	19	669	23
2007-2011	266	5	814	17
Year of initial stroke unknown	0	0	0	0
Risk factors				
No hypertension	487	23	980	39
Hypertension	842	39	1760	83
Hypertension unknown	104	1	118	2
No antihypertensive medication	81	16	765	30
Anti-hypertensive medication at 3m	71	14	1054	55
Unknown anti-hypertensive medication	1281	33	1039	39
Stroke severity				
GCS <13	826	10	356	9
13-15	534	51	2390	111
GCS unknown	73	2	112	4
Process of care				
Not admitted to hospital	93	10	391	27
Admitted to general medical ward	769	26	875	45
Admitted to Stroke Unit	547	27	1529	51
Unknown	24	0	63	1

(ii) 1-5 years after first stroke

	Number died - no recurrence	Number died - with recurrence	Number censored – no recurrence	Number censored – with recurrence	Number in study– at end of time-period – no recurrence	Number in study at end of time-period – with recurrence
Total	679 (22.1)	109 (3.6)	505 (19.3)	8 (0.3)	1525 (49.7)	156 (5.1)
Age group						
<65	105	15	254	3	737	74
65-74	179	30	103	2	449	46
>75	395	64	148	3	339	36
Age group unknown	0	0	0	0	0	0
Gender						
Male	334	59	276	5	874	85
Female	345	50	229	3	651	71
Gender unknown	0	0	0	0	0	0
Ethnicity						
White	535	79	292	4	975	95
Black	103	23	175	3	404	47
Other	29	6	36	1	116	11
Ethnicity unknown	12	1	2	0	30	3
Socio economic status						
Non-manual	185	31	185	5	468	39
Manual	413	72	200	2	870	103
Unknown	14	0	48	1	97	8
Economically inactive	67	6	72	0	90	6
Stroke Subtype						
Infarct	594	94	406	6	1172	118

PICH	50	6	37	1	184	24
SAH	6	1	13	0	105	6
Stroke subtype unknown	29	8	49	1	64	8
Year of initial stroke						
1995-1998	234	47	0	0	433	71
1999-2002	155	34	0	0	439	46
2003-2006	163	21	0	0	481	27
2007-2011	127	7	505	8	172	12
Year of initial stroke unknown	0	0	0	0	0	0
Risk factors						
No hypertension	204	26	192	3	550	44
Hypertension	444	80	306	5	904	104
Hypertension unknown	31	3	7	0	71	8
No antihypertensive medication	216	28	174	2	339	36
Anti-hypertensive medication at 3m	252	42	125	2	623	65
Unknown anti-hypertensive medication	211	39	206	4	563	55
Stroke severity						
GCS <13	90	10	67	0	188	10
13-15	565	94	411	7	1287	137
GCS unknown	24	5	27	1	50	9
Process of care						
Not admitted to hospital	77	32	37	0	238	34
Admitted to general medical ward	250	39	49	1	517	64
Admitted to Stroke	342	38	391	7	746	56

Unit						
Unknown	11	0	28	0	24	2

(iii) 5-10 years after first stroke

	Number died - no recurrence	Number died - with recurrence	Number censored – no recurrence	Number censored – with recurrence	Number in study– at end of time-period – no recurrence	Number in study at end of time-period – with recurrence
Total	356 (21.2)	85 (5.1)	525 (31.2)	30 (1.8)	599 (35.6)	87 (5.2)
Age group						
<65	75	19	285	20	365	47
65-74	123	34	139	5	163	31
>75	158	32	101	5	70	9
Age group unknown	0	0	0	0	0	0
Gender						
Male	194	44	300	14	355	52
Female	41	41	225	16	243	35
Gender unknown	0	0	0	0	0	0
Ethnicity						
White	279	61	305	13	360	52
Black	48	21	161	14	183	24
Other	21	2	48	2	44	10
Ethnicity unknown	8	1	11	1	10	1
Socio economic status						
Non-manual	108	29	152	9	191	18
Manual	209	51	295	17	340	61
Unknown	10	0	40	3	46	6
Economically inactive	29	5	38	1	21	2

Stroke Subtype						
Infarct	289	71	406	17	440	67
PICH	46	10	60	6	74	12
SAH	7	0	30	5	67	2
Stroke subtype unknown	14	4	29	2	17	6
Year of initial stroke						
1995-1998	144	55	0	0	255	50
1999-2002	133	24	0	0	295	33
2003-2006	76	6	356	18	48	4
2007-2011	3	0	169	12	0	0
Year of initial stroke unknown	0	0	0	0	0	0
Risk factors	107	26	194	11	235	21
No hypertension	229	57	328	18	317	59
Hypertension	20	2	3	1	46	7
Hypertension unknown						
No antihypertensive medication	98	16	62	4	172	23
Anti-hypertensive medication at 3m	165	45	208	12	228	30
Unknown anti-hypertensive medication	93	24	255	14	198	34
Stroke severity						
GCS <13	43	2	65	4	79	5
13-15	301	80	444	23	499	77
GCS unknown	12	3	16	3	20	5
Process of care						
Not admitted to hospital	55	18	58	2	115	24
Admitted to general	133	36	36	10	282	37

medical ward						
Admitted to Stroke Unit	164	30	30	18	197	23
Unknown	4	1	1	0	4	3

(iv) 10-15 years after first stroke

	Number died - no recurrence	Number died - with recurrence	Number censored – no recurrence	Number censored – with recurrence	Number in study– at end of time-period – no recurrence	Number in study at end of time-period – with recurrence
Total	103 (15.0)	32 (4.7)	342 (49.9)	32 (4.7)	148 (21.6)	29 (4.2)
Age group						
<65	40	10	224	20	100	18
65-74	37	18	84	9	38	8
>75	26	4	34	3	9	3
Age group unknown	0	0	0	0	0	0
Gender						
Male	61	21	200	17	90	18
Female	42	11	142	15	57	11
Gender unknown	0	0	0	0	0	0
Ethnicity						
White	71	21	190	17	95	18
Black	21	9	118	8	42	9
Other	9	2	26	6	9	2
Ethnicity unknown	2	0	8	1	1	0
Socio economic status						
Non-manual	27	10	118	7	41	6
Manual	66	21	178	20	95	21
Unknown	5	1	34	4	6	1
Economically	5	0	12	1	4	1

inactive						
Stroke Subtype						
Infarct	83	26	247	22	105	24
PICH	10	4	44	5	19	4
SAH	6	1	42	1	19	0
Stroke subtype unknown	4	1	9	4	4	1
Year of initial stroke						
1995-1998	74	24	28	3	147	29
1999-2002	29	8	266	25	0	0
2003-2006	0	0	48	4	0	0
Year of initial stroke unknown	0	0	0	0	0	0
Risk factors						
No hypertension	25	6	145	10	63	7
Hypertension	69	26	167	17	77	20
Hypertension unknown	9	0	30	5	7	2
No antihypertensive medication	38	7	63	4	71	12
Anti-hypertensive medication at 3m	38	11	133	11	53	12
Unknown anti-hypertensive medication	27	14	146	17	23	5
Stroke severity						
GCS <13	17	1	42	1	20	3
13-15	84	29	287	28	124	24
GCS unknown	2	2	13	3	3	2
Process of care						
Not admitted to hospital	27	12	55	6	32	7

Admitted to general medical ward	48	13	134	11	97	16
Admitted to Stroke Unit	27	7	150	13	18	5
Unknown	1	0	3	2	0	1